# Management of Urothelial Carcinoma

Ja Hyeon Ku
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# Part I

# Non-muscle Invasive Bladder Cancer

# 1 Epidemiology, Etiology, and Histopathology

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## 1.1 Epidemiology

Bladder cancer is the second most common urologic cancer and ninth most common malignancy worldwide. Prevalence of bladder cancer is relatively higher in developed countries [1–3] (Fig. 1.1, Table 1.1). Age-standardized rate (ASR; per 100,000 person/years) of incidence was higher in Europe (21.8 in Southern; 19.7 in Western; 15.1 in Central and Eastern), Northern America (19.5), Western Asia (19.0), and Northern Africa (15.1) [2].

The incidence is more than three times higher in the male population; ASR was 2.2 in male and 0.9 in female. The differences of bladder cancer incidence rate between sexes are variable between countries about tenfold variation [2]. Bladder cancer incidence increases with age, with more than 60% of disease diagnosed in the elderly (the age 65 and more) [2]. The cumulative risk to age 75 was 0.6% in both sexes combined analysis [1].

According to Globocon, estimated bladder cancer-related death is 165,000 worldwide, and there was no difference between less and more developed countries (Fig. 1.2). ASR of mortality was higher in male population; 9.0 for men and 2.2 for women [1]. Turkey ranks the highest mortality among men, more than 1.5 times higher than Europe and 3 times higher than the United States [2].

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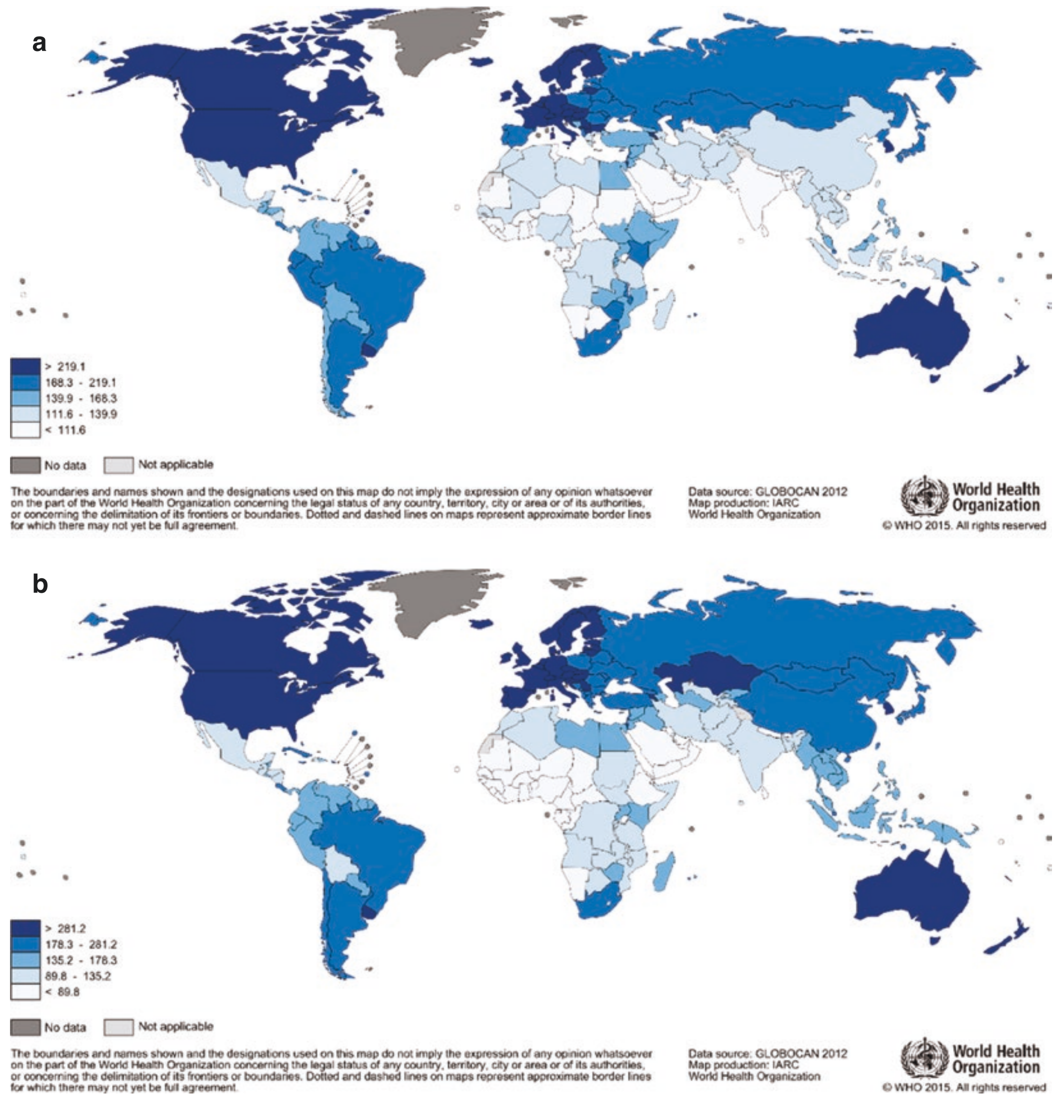
a
> 219.1
168.3 - 219.1
139.9 - 168.3
111.6 - 139.9
< 111.6
No data
Not applicable
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.
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Map production: IARC
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b
> 281.2
178.3 - 281.2
135.2 - 178.3
89.8 - 135.2
< 89.8
No data
Not applicable
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**Fig. 1.1** Estimated age-standardized incidence rate (per 100,000) in male (**a**) and female (**b**) populations among 184 countries in 2012. Copyright from Elsevier Publisher [1]

**Table 1.1** More developed regions are all regions of Europe plus Northern America, Australia, New Zealand, and Japan

| | | *N* (×100,000) | | Age-standardized rate (per 100,000 population) | | Cumulative risk (%) | |
|---|---|---|---|---|---|---|---|
| Region | | Incidence | Mortality | Incidence | Mortality | Incidence | Mortality |
| World | Men | 3303 | 1230 | 9 | 3.2 | 1 | 0.3 |
| | Women | 994 | 420 | 2.2 | 0.9 | 0.2 | 0.1 |
| More developed regions | Men | 1960 | 589 | 16.9 | 3.7 | 2.0 | 0.4 |
| | Women | 577 | 210 | 3.7 | 1.1 | 0.4 | 0.1 |
| Less developed regions | Men | 1343 | 641 | 5.3 | 2.6 | 0.6 | 0.2 |
| | Women | 416 | 210 | 1.5 | 0.7 | 0.2 | 0.1 |

Less developed regions are all regions of Africa, Asia (excluding Japan), Latin America and the Caribbean, Melanesia, Micronesia, and Polynesia

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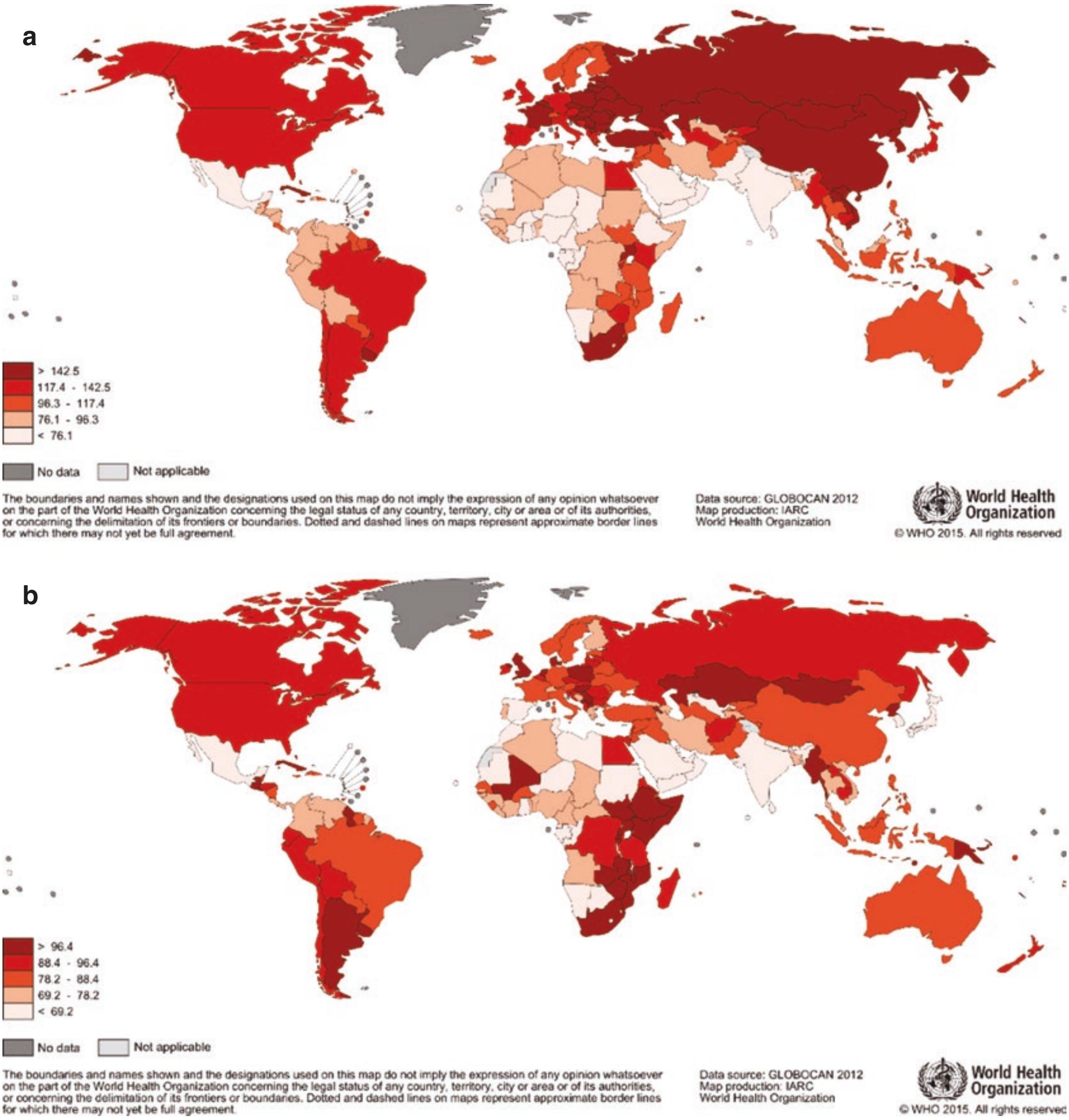
a
> 142.5
117.4 - 142.5
96.3 - 117.4
76.1 - 96.3
< 76.1
No data
Not applicable
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b
> 96.4
88.4 - 96.4
78.2 - 88.4
69.2 - 78.2
< 69.2
No data
Not applicable
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**Fig. 1.2** Estimated age-standardized mortality rate (per 100,000) in male (**a**) and female (**b**) populations among 184 countries in 2012. Copyright from Elsevier Publisher [1]

## 1.2 Etiology

### 1.2.1 Genetic Factors

Several genetic factors are important in the development of bladder cancer. Most of the genetic alterations associated with bladder cancer were somatic mutation; thus typically bladder cancer is not inherited [4]. Numerous genetic and epigenetic alterations of bladder cancer are discovered recently due to advanced DNA sequencing technology.

Some chromosomal rearrangement is associated with bladder cancer carcinogenesis. Cytogenetic analysis founded loss of chromosome 9 [5, 6] and 11p, 8p are frequently founded in bladder cancer [7]. Principal component analysis of 200 bladder urothelial carcinoma chro-

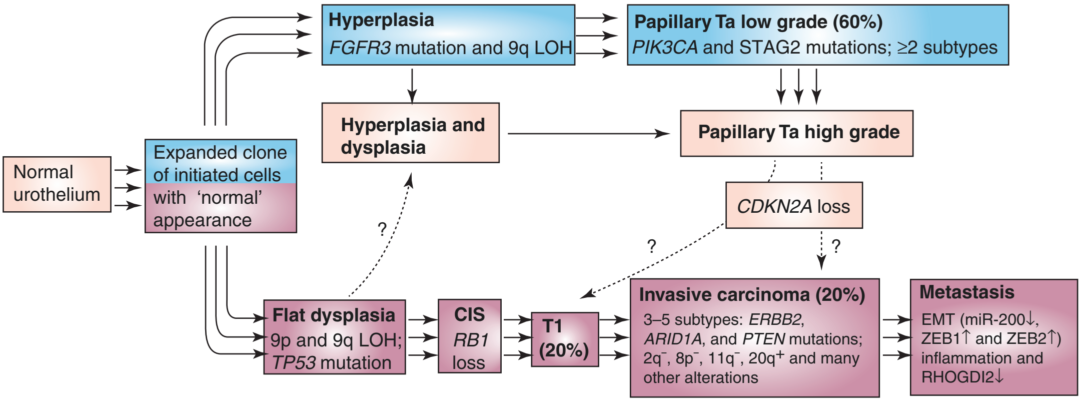
Hyperplasia
FGFR3 mutation and 9q LOH
Papillary Ta low grade (60%)
PIK3CA and STAG2 mutations; ≥2 subtypes
Hyperplasia and dysplasia
Papillary Ta high grade
Normal urothelium
Expanded clone of initiated cells with 'normal' appearance
CDKN2A loss
?
?
?
Flat dysplasia
9p and 9q LOH; TP53 mutation
CIS
RB1 loss
T1 (20%)
Invasive carcinoma (20%)
3–5 subtypes: ERBB2, ARID1A, and PTEN mutations; $2q^{-}$, $8p^{-}$, $11q^{-}$, $20q^{+}$ and many other alterations
Metastasis
EMT (miR-200↓, ZEB1↑ and ZEB2↑) inflammation and RHOGDI2↓

**Fig. 1.3** Potential genetic pathway of urothelial carcinoma. There were two major possible pathways with distinct pathologic and molecular feature. Copyright from Springer-Nature Publisher [8]

mosomal aberrations [7] acquired from Mitelman Database of Chromosome Aberrations in Cancer identified two cytogenetic pathways, one initiated by −9 and followed by −11p and 1q− and the other initiated by +7 and followed by 8p− and −8q. Gain of 7 chromosome pathway related with more aggressive bladder cancer however in later stage contain a common set of imbalances. NMIBC have few genomic changes and almost diploid karyotype; however, muscle-invasive bladder cancer (MIBC) has many genomic alterations and aneuploidy karyotypes [8].

FGFR, TP53, and PI3K gene mutations are important pathways in bladder cancer carcinogenesis [4]. In NMIBC, FGFR is the most common genomic alteration. Approximately 80% of NMIBC has mutation in FGFR3 gene [9, 10] and is related with favorable prognosis [9]. A SNP in TACC3 intron, which 70 kb from FGFR3 indicate higher risk of recurrence in low-grade stage Ta tumor [11]. Most of bladder cancer. TP53 gene, which encodes the p53 tumor suppressor gene, is related to high-stage, high-grade tumor and frequently found in muscle-invasive bladder cancer (MIBC) [12]. TP53 mutation in bladder cancer is positively related to smoking [13]. TP53 and FGFR mutations are almost mutually exclusive [12]. PI3K pathway alteration founded up to 42% of all bladder cancer [14]. PIK3CA mutation is relatively common in NMIBC, occurring in up to 25% of the disease [8]. PTEN, which negatively regulates PI3K, is commonly found in LOH in MIBC (Fig. 1.3) [8].

### 1.2.2 Environmental Factors

Tobacco smoking [15] and occupational exposure to chemical materials [16], especially in aromatic amine compounds, are well-established risk factors of bladder cancer. Radiotherapy is also considered as potential risk factor for secondary bladder cancer; however, there are still controversies [17, 18]. Some dietary factors are also considered as potential risk factors of bladder cancer, but there are still not enough evidences. Bladder schistosomiasis and chronic urinary tract infection are associated with bladder urothelial carcinoma and progress to squamous cell carcinoma [19, 20].

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# Histopathology

# 2

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## 2.1 Urothelial Carcinoma

Predominant histological subtype of bladder malignancy is urothelial carcinoma [1]. About 90% of bladder cancers are urothelial carcinoma, 5% are squamous cell carcinoma, and less than 2% are adenocarcinoma or other variants. Squamous cell carcinoma predominates in Middle East counties where schistosomiasis is endemic. Females with recurrent infection or chronic indwelling catheters in Western counties reveal higher incidence of squamous cell carcinoma [2]. About 80% of patients are diagnosed with non-muscle invasive bladder cancer (NMIBC) at initial diagnosis.

In NMIBC, histologic grading is the most important prognostic factor. The WHO grading system modified criteria of histologic grade in NMIBC at 2004, categorized by papillary urothelial neoplasm of low malignant potential (PUNLMP) and low-grade and high-grade urothelial cancer.

PUNLMP composed 50% of NMIBC and is characterized by papillary growth of urothelium with minimal cytological atypia [3] (Fig. 2.1, Table 2.1). PUNLMP can recur in 35% and grade

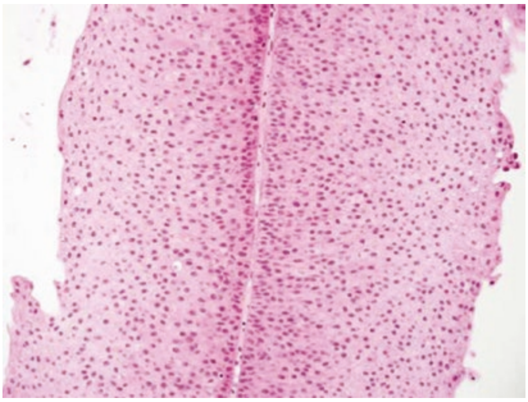

**Fig. 2.1** Papillary urothelial neoplasm of low malignant potential. The urothelium is thickened with only minimal cytological and architectural atypia. Copyright from Springer-Nature Publisher [3]

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**Table 2.1** Architecture and nuclear features of each histologic group of urothelial carcinoma

| | PUNLMP | Low grade | High grade |
|---|---|---|---|
| *Architectural character* | | | |
| Papillae | Rarely fused | Occasionally fused | Fused and branching |
| Organization | Polarity normal | Predominantly ordered with minimal crowding and loss of polarity | Predominantly disordered with crowding, overlapping cells, and loss of polarity |
| | Any thickness | Any thickness | Any thickness—may be single cells (denuding) |
| | Most increased cohesive cells | Most increased cohesive cells | Often discohesive |
| *Nuclear feature* | | | |
| Size | Mildly enlarged | Enlarged | Enlarged |
| | Uniform | Some variation | Marked variability |
| Shape | Elongated | Elongated-oval-round | Pleomorphic |
| | Uniform | Slight variation | |
| Chromatin | Fine | Fine with some variation | Frequently coarse with marked variation |
| Nucleoli | Fine | Usually inconspicuous | Prominent |
| | | | Single to multiple |
| Mitoses | Rare | Infrequent | Frequent |
| | Basal if present | Most basal if present | Any level |

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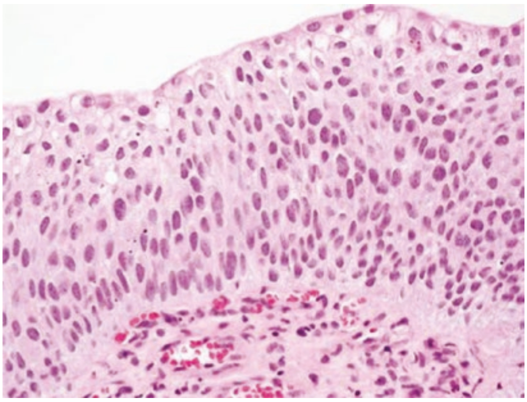

**Fig. 2.2** Low-grade papillary urothelial carcinoma. The urothelium is thickened with the architecture generally intact but with some irregularity in the nuclear spacing. There is variability in the nuclear size with variable degrees of hyperchromasia. Copyright from Springer-Nature Publisher [3]

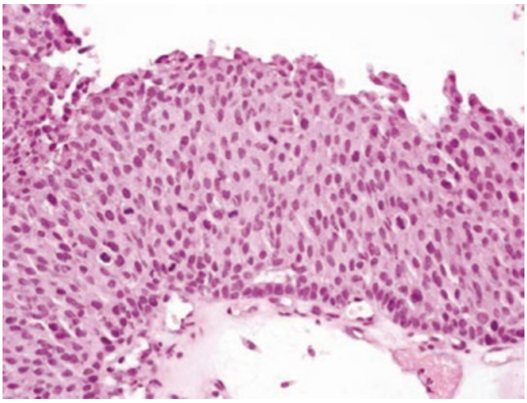

**Fig. 2.3** High-grade papillary urothelial carcinoma. The urothelium has increasing architectural irregularity and mild to moderate cytological atypia. There are numerous mitotic figures scattered throughout the urothelium. Copyright from Springer-Nature Publisher [3]

progress in 11% of case but rarely in stage progression. Low-grade urothelial cancer consists 25% of NMIBC and histologically differs from PUNLMP, characterized by multiple stalks, more increased cellular size, nuclear atypia, and mitotic figure (Fig. 2.2, Table 2.1) [3]. High-grade urothelial cancer shows fused papillary stalk and numerous mitotic features (Fig. 2.3, Table 2.1) [3]. Both low- and high-grade urothelial cancers recur over a half of patients; however stage progression is higher in high-grade cancer, which occurs in about 50% of cases.

### 2.1.1 Carcinoma In Situ

Carcinoma in situ (CIS) is characterized by a flat, high-grade, noninvasive urothelial carcinoma [4] which has aggressive characteristics (Fig. 2.4). CIS

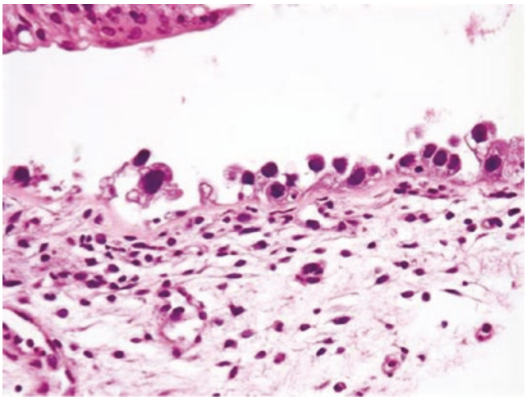

**Fig. 2.4** Urothelial carcinoma in situ. The denuding pattern is characterized by poorly cohesive cells that typically have large, pleomorphic, and hyperchromatic nuclei. Copyright from Springer-Nature Publisher [3]

shows higher chance of invasion, metastasis, and recurrence. CIS may present with or without synchronous urothelial cell carcinoma, and it can occur at any site of the urinary tract. Detection is the most challenging part of management of CIS, because of low sensitivity of diagnostic methods. The sensitivity of each diagnostic method is reported to be 60% in urine cytology, 77% in multiple random biopsies, and 23–68% in white light cystoscopy [5].

### 2.1.2 Lymphovascular Invasion

Lymphovascular invasion (LVI) is defined as presence of a tumor cell in the lymphatic vessels or blood vessels (Fig. 2.5). The negative prognostic

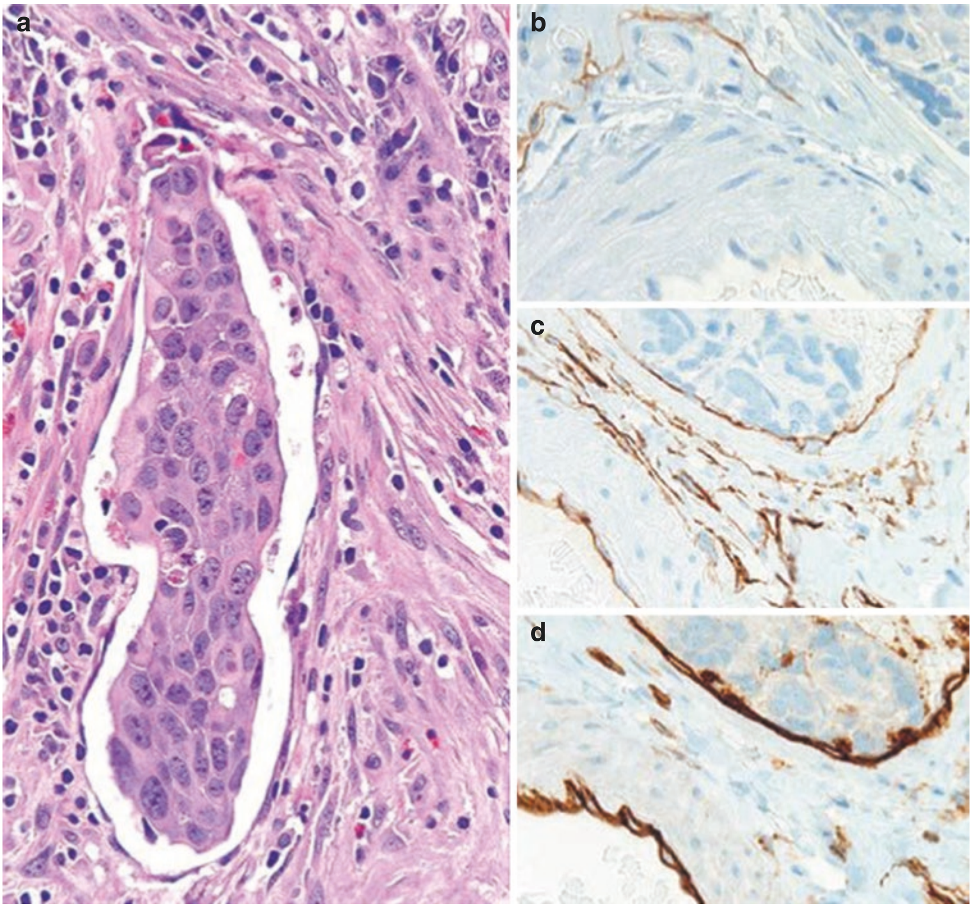

**Fig. 2.5** (**a**) Urothelial cancer within a vascular space stained with hematoxylin and eosin. (**b**) Podoplanin immunohistochemistry staining the endothelium of lymphatic vessels (arrows). (**c**) CD34 immunohistochemistry and (**d**) CD31 immunohistochemistry staining blood vessel endothelial cells as a proof of tumor (T) invasion into blood vessels (arrow heads). All images at 400× magnification. Copyright from Springer-Nature Publisher [6]

role of LVI is well established in muscle invasive bladder cancer (MIBC). Presence of LVI is related to aggressive disease, such as increased T stage, tumor grade, and lymph node metastasis in patients treated with radical cystectomy [7–9]. LVI is also associated with disease recurrence [9, 10] and cancer-specific mortality [11, 12].

The prognostic role of LVI in non-muscle invasive bladder cancer (NMIBC) is still under discussion. Most studies agreed that the presence of LVI in TURBT specimen is associated with disease recurrence and progression [13, 14]; however some studies show disparate evidences [15, 16]. Recent meta-analysis study [17] shows LVI in TURBT specimen of MIBC associated with recurrence-free survival (1.28, 95% CI 1.34–2.46) and progression-free survival (HR 2.28, 95% CI 1.45–3.58). Green et al. [18] report presence of LVI in TURBT specimen predicts non-organ confined bladder cancer at radical cystectomy specimen with sixfold higher risk. Current evidence supports that patients with LVI in T1 high-grade bladder cancer have benefit from undergoing early radical cystectomy.

### 2.1.3 Histologic Variant of Urothelial Carcinoma

Histological variants of urothelial carcinoma in the bladder are frequently found, and some of them predict poor prognosis [19]. Squamous and glandular differentiations are the most common histologic variants of urothelial carcinoma which account up to 60% of cases (Figs. 2.6 and 2.7)

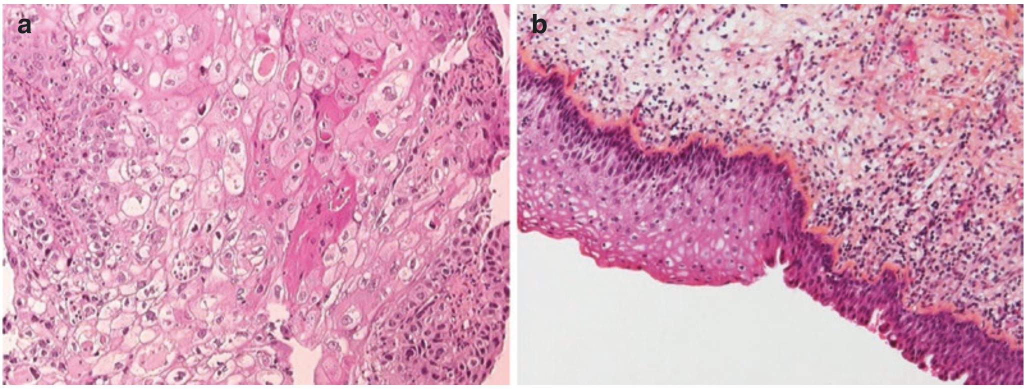

**Fig. 2.6** Squamous cell carcinoma. (**a**) Squamous cell carcinoma with intracellular bridges and keratinization. (**b**) Squamous cell metaplasia (HES, magnification ×40). Copyright from Springer-Nature Publisher [20]

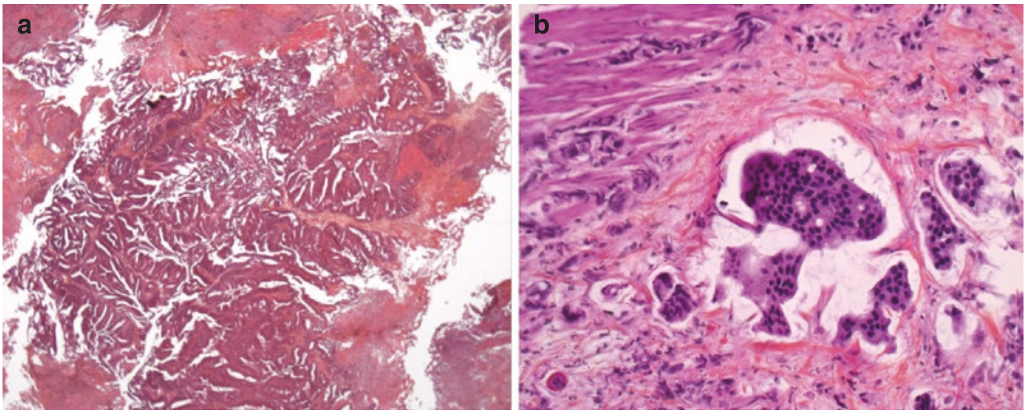

**Fig. 2.7** Glandular variant. (**a**) Resection specimen of an enteric adenocarcinoma (hematoxylin, eosin, and saffron stain (HES), magnification ×25). (**b**) The mucinous type (HES, magnification ×200). Copyright from Springer-Nature Publisher [20]

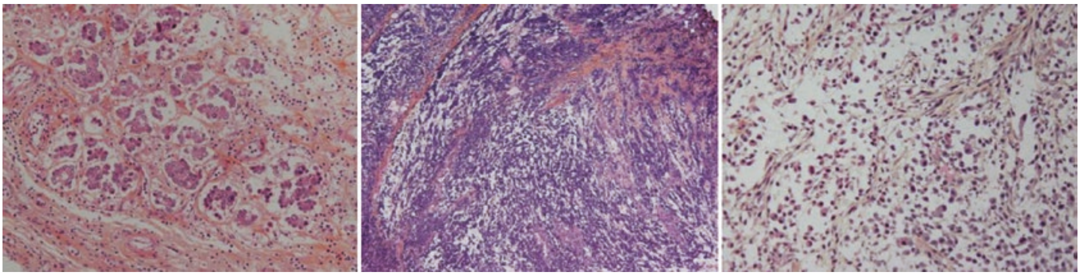

**Fig. 2.8** Micropapillary variant. (Left) The empty spaces around the tumor cells can be mistaken for lymphovascular invasion. Immunohistochemistry can be helpful in the differential diagnosis (hematoxylin, eosin, and saffron stain, magnification ×200). Sarcomatoid carcinoma (middle) fusiform cells with poorly differentiated fascicles, destroying the underlying bladder wall (hematoxylin, eosin, and saffron stain, magnification ×50). Plasmacytoid variants. (Right) Tumor cells look similar to plasma cells; they invade the bladder wall in a diffuse manner (hematoxylin, eosin, and saffron stain, magnification ×100). Copyright from Springer-Nature Publisher [20]

[21]. Histologic variants in NMIBC are related to higher recurrence rate and progression than conventional urothelial carcinoma. Most histologic variants need more aggressive treatment. Even some highly aggressive variants (micropapillary, sarcomatoid, and plasmacytoid carcinoma) or non-urothelial variants of bladder cancer need early radical cystectomy, even in NMIBC (Fig. 2.8).

### 2.1.4 T1 Sub-staging

Characteristics and prognosis of T1 urothelial carcinoma vary by grade, size, multiplicity, and presence of concomitant CIS [22]. Value of T1 sub-staging is still under investigation, but recent study shows significant information for determining prognosis of T1 bladder tumor.

Martin-Doyle et al. [23] using T1 sub-staging system and muscularis mucosae (MM) as a landmark revealed that patients with T1b (infiltrate MM but not passed) and T1c (passing through MM) show more aggressive features. van Rhijn et al. [22] using another sub-staging system of divide T1-microinvasive (T1m) and T1-extensive-invasive (T1e) tumor and successfully shows clinical significance of T1 sub-staging for predict prognosis. T1m shows more aggressive feature with 83% of 5-year progression rate than T1e tumor (55%).

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# Symptoms and Work-Up

3

Jungyo Suh

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## 3.1 Hematuria

### 3.1.1 Diagnostic Value of Hematuria

Hematuria is the most common symptom of bladder cancer. About 90% of bladder cancer patients present with hematuria at the time of diagnosis, which is either gross or microscopic [1]. Gross hematuria is more strongly correlated with advanced bladder cancer [2].

Screening of hematuria in the general population is still not recommended. Gross hematuria is relatively common; prevalence was almost 2.5% in the community population and 4–20% in urologic visit population [3]. Jones et al. [4] reviewed the UK General Practice Research Database and reported 3-year positive predictive value (PPV) of hematuria was 7.4% (95%, CI 6.8–8.1%) in men and 3.4% (95%, CI 2.9–4.0%) in women. However, PPV of hematuria in patients younger than 45 years old was only 0.99% (0.53–1.69%) in men and 0.22% (95%, CI 0.05–0.64) in women. There was no qualified evidence [5] and not cost-effective [6], routine screening of microscopic hematuria with dipstick is not recommended even in the high risk population.[7].

Many diseases can cause gross or microscopic hematuria. Incidence of urinary tract malignancy in hematuria patients is only 0.4% in children to 22.5% in adult population [8]. Not all hematuria patients need diagnostic work-up; however specific populations like the male gender and medical history like cigarette smoking and occupational exposure of carcinogen need further evaluation. About 70–90% of microscopic hematuria and 50% of gross hematuria patients visiting primary care center undergone nondiagnostic evaluation [9]. Thus, diagnostic work-up should proceed with step-by-step approaches (Fig. 3.1) within selective, high-risk populations.

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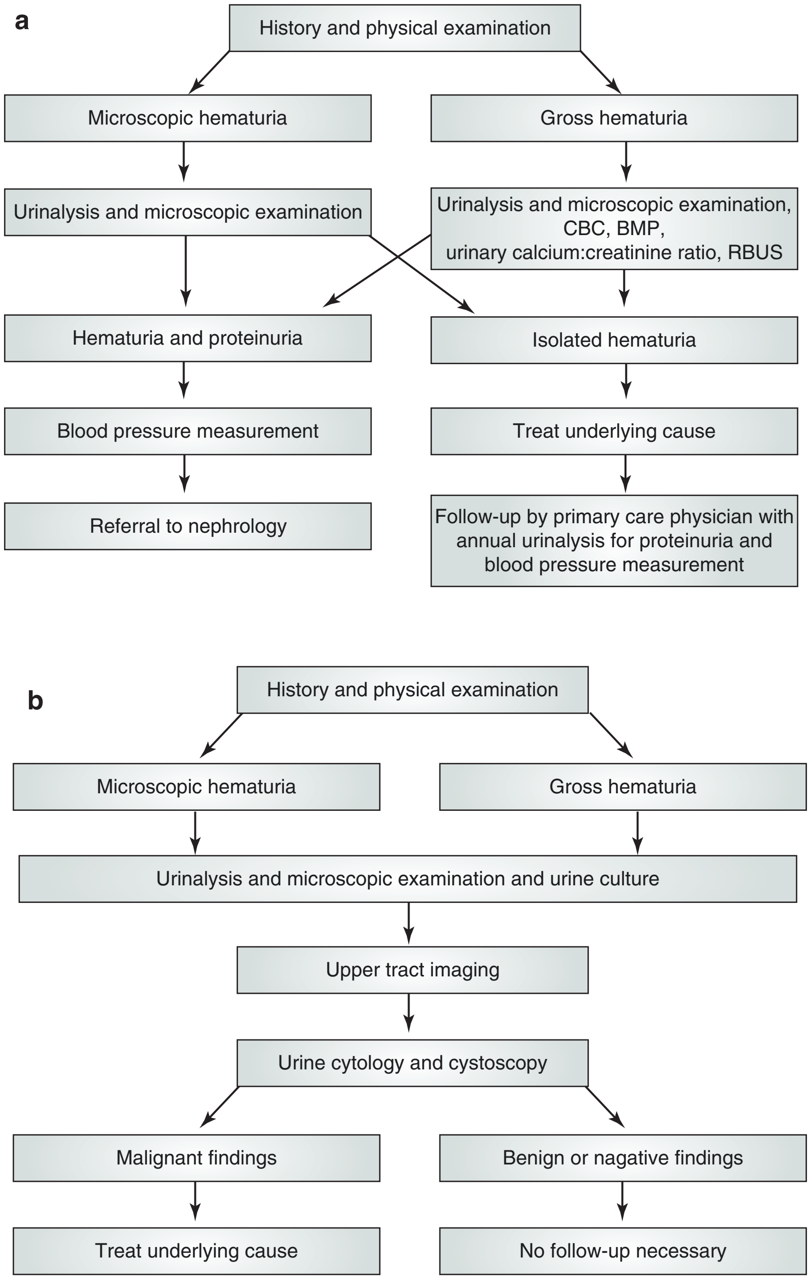
a
History and physical examination
Microscopic hematuria
Gross hematuria
Urinalysis and microscopic examination
Urinalysis and microscopic examination, CBC, BMP, urinary calcium:creatinine ratio, RBUS
Hematuria and proteinuria
Isolated hematuria
Blood pressure measurement
Treat underlying cause
Referral to nephrology
Follow-up by primary care physician with annual urinalysis for proteinuria and blood pressure measurement
b
History and physical examination
Microscopic hematuria
Gross hematuria
Urinalysis and microscopic examination and urine culture
Upper tract imaging
Urine cytology and cystoscopy
Malignant findings
Benign or nagative findings
Treat underlying cause
No follow-up necessary

**Fig. 3.1** The evaluation begins with a thorough history and physical examination to determine any characteristics that would suggest an etiology for the hematuria. Urinalysis with microscopic examination is performed to confirm the presence of hematuria and to evaluate for proteinuria. Proteinuria should be confirmed with a spot urine protein/creatinine ratio or a 24-h urine collection for total protein. The diagnosis of hematuria and proteinuria suggests glomerular disease that should be referred to a nephrologist. Isolated hematuria should be treated on the basis of the underlying cause, and the patient should be followed up with annual urinalysis and blood pressure measurement. (**b**) Adults. The evaluation begins with a thorough history and physical examination to determine any characteristics that would suggest an etiology of the hematuria. Urinalysis with microscopic examination is performed to confirm the presence of hematuria. A urine culture should be performed to evaluate for coexisting urinary tract infection that requires treatment before cystoscopy. Evaluation of the upper tracts by imaging with CT intravenous pyelography as available should be done before cytology and cystoscopy. Patients with a negative work-up do not need follow-up unless they develop recurrent hematuria. *BMP* basic metabolic panel, *CBC* complete blood count, *RBUS* renal bladder ultrasonography. Copyright from Springer-Nature Publisher [8]

### 3.1.2 Gender Difference and Hematuria (SEER DB)

Bladder cancer occurs three times frequently in men; however, women present more advanced disease and poor prognosis [10]. Understanding gender differences of bladder cancer etiology, biology, and outcome should provide better oncological outcome to bladder cancer patients. Hematuria is one of the most important symptoms urologists face in the outpatient clinic, and loss of timing to intervention is more crucial in female bladder cancer patients.

A study using SEER (Surveillance, Epidemiology, and End Results) cancer database for analysis of gender difference in hematuria evaluation [11] shows that time to visit urology clinic was longer (adjusted HR 0.9, 95% CI 0.87–0.92) and delayed hematuria evaluation was higher (adjusted OR 1.13, 95% CI 1.07–1.21) in female than male patients. Median time to first visit urology clinic was 2 days for men and 6 days for women. Median time for initiating hematuria evaluation was similar in both sexes, but delay over 1 month for evaluation of any component was higher in female. This finding related with that women may take more circuitous route through the healthcare system before seeing a urologist, because of they might visit primary care physician or obstetrician/gynecologist at initial hematuria presentation [11].

There is another study using SEER database which showed delay in the diagnosis affects bladder cancer mortality because of advanced stage and histology; however after adjustment of this prognostic factor does not eliminated hazard ratio of women population [12]. At this point, prognostic effect of delayed diagnosis of women needs future investigation.

### 3.1.3 Asymptomatic Microscopic Hematuria

Asymptomatic microscopic hematuria (AMH) is a common symptom when patients visit urologic clinic. Most of the guidelines defined AMH as three or more RBCs per high-power microscopic field (HPF) on a properly collected urine [13]. Although screening using urine dipstick test for bladder cancer is generally not recommended, the prevalence of incidentally founded microscopic hematuria is about 2–31% [14] in adults and 0.5–2% in children [8].

In many cases with microscopic hematuria, pathologic cause of bleeding could not be found after diagnostic work-up. Less than 5% of patient with microscopic hematuria has urinary malignancy. The long-term observation study of Japan shows that most of microscopic hematuria cases show 45% of symptoms disappeared after follow-up [15]. Evidence of UTI in microscopic hematuria patients should be rechecked through urinalysis 6 weeks after antibiotic treatment.[13] If hematuria is resolved after treatment, no further evaluation is needed.

Sensitivity of urine dipstick test for detecting microscopic hematuria is as high as 90%; however a false-positive result can occur in specific conditions, such as hemoglobinuria, myoglobinuria, and high-pH urine. Patients consuming vitamin C can have a false-negative result in dipstick test, so patients in this situation need to proceed with microscopic urinalysis for evaluation of hematuria [16]. Rao et al. [17] show that within 91 patients with dipstick positive, only 22 patients (22%) have positive results in microscopic urinalysis, and only one of them had a malignancy. Although dipstick test is highly sensitive and easy to use, confirmative microscopic urinalysis should always be done before hematuria evaluation.

The major etiology of hematuria is quite different from children to adult. Unlike adult population finding malignancy during initial hematuria evaluation is low, and most of them are not UCC but Wilms tumor [8]. For this reason, cystoscopy is not always indicated for evaluation of hematuria in children. Hematuria origin of glomerular or non-glomerular is essential for initial diagnosis in children. If microscopic hematuria is present with proteinuria, renal disease is suggested, and patient should be referred to the nephrology department [8]. Usage of imaging and cystoscopy for hematuria evaluation is not established. Unlike adult patients, children with hematuria but negative result in initial evaluation should have annual reevaluation of urinalysis, and blood pressure measurement is recommended.

## 3.2 Lower Urinary Tract Symptoms

Carcinoma in situ (CIS) and muscle-invasive bladder cancer can present with irritative voiding symptoms, such as dysuria, frequency, urgency, feeling of incomplete emptying, and nocturia. About 20% of irritative voiding symptoms are associated with CIS lesion [18]. Asymptomatic microscopic hematuria is sometimes related to CIS [19]. A palpable mass on bimanual examination provides information of clinical stage and muscle invasiveness; however it is not easy to perform in outpatient clinics.

Obstructive symptoms are commonly caused by benign condition such as benign prostatic hypertrophy or bladder stone; if there are no other definite causes of urinary symptoms, diagnostic work-up should be needed. Sometimes advanced bladder lesion of urothelial carcinoma can cause obstructive symptoms.

## 3.3 Modalities for Upper Tract Evaluation

Clinical application of imaging modality in evaluation of urothelial carcinoma intravenous urography (IVU) is commonly used for upper urinary evaluation; however estimated detection rate is only 60% of bladder cancer and 66% of upper tract tumor by studies [20]. IVU has limitation in detecting carcinoma in situ lesions and high false-positive rate of benign lesion.

The current diagnostic modality of choice in hematuria patients is CT urography [21]. Diagnostic efficacy of CT urography for detecting bladder malignancy ranged from 79 to 93%, 94 to 99%, and 75 to 98% in sensitivity and specificity. CT urography using contrast media to obtain excretory phase provides high detection rate of urinary tract malignancy. The major limitation of CT urography is that it cannot differentially diagnose small malignant lesions [22] and has high radiation exposure during examination. For this reason, the expert suggested diagnostic strategies with the risk score system for favor perform CT urography [21]. This risk score system and diagnostic strategy is not considered as standard, but useful for decision making when physician meet hematuria patients in out-patients setting (Fig. 3.2, Table 3.1).

MRI and advanced MRI technique (diffusion weighted, gadolinium enhancing) also shows good result, however limited to detect CIS lesion and low incidence of concomitant upper tract abnormality, some of guidelines does not recommend upper tract imaging work up at initial diagnosis [23]. Transabdominal ultrasonography is useful for detecting hydronephrosis and intraluminal mass, but it cannot replace CT urography [24]. Ureteroscopic exam makes direct visualization of ureter abnormality but is not recommended in routine examination. Selective ureter cytology can provide information of upper tract malignancy, but it shared low sensitivity problem of cytology in low-grade tumor.

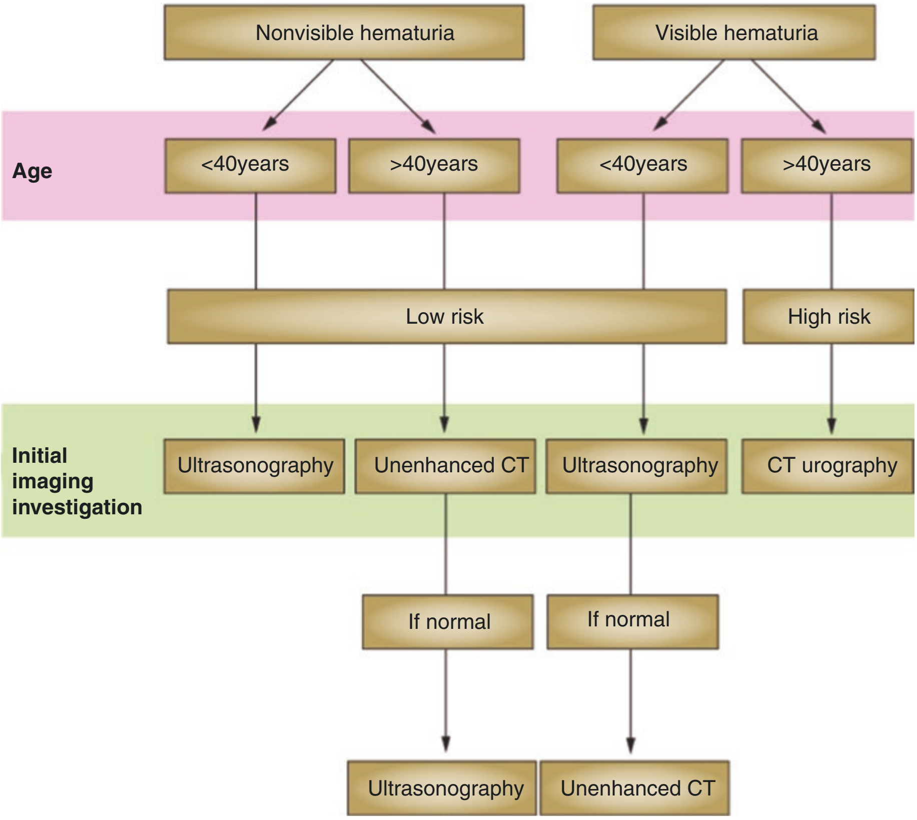

**Fig. 3.2** A summary of diagnostic strategies for investigating hematuria. Patients should undergo imaging investigations according to their risk of urothelial cell carcinoma, which depends on age and whether hematuria is visible. Copyright from Springer-Nature Publisher [21]

**Table 3.1** If patient with sum of risk score over 3 favors perform enhanced CT (CT urography) than non-enhanced CT or ultrasonography, because those kind of patients shows higher risk of malignant lesion

| Risk factor | Risk score |
|---|---|
| ≥40 years of age | 1 |
| *Hematuria* | |
| Visible | 2 |
| Nonvisible, persistent | 1 |
| Nonvisible, unspecified | 0 |
| *Imaging findings* | |
| UUT-UCC | 2 |
| Bladder cancer | 2 |
| Renal mass | 2 |
| Hydronephrosis, hydroureter | 2 |
| Stone, large, for planning percutaneous nephrolithotomy | 2 |
| *Urine cytology* | |
| Normal, atypical probably benign, atypia of uncertain significance | 0 |
| Atypia suspicious of malignancy and malignant | 2 |
| Occupational exposure to aromatic amines or benzenes, smoking, analgesic abuse, phenacetin | 2 |
| Urethral stricture preventing cystoscopy | 2 |

*UCC* urothelial cell carcinoma, *UUT-UCC* upper urinary tract urothelial cell carcinoma
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# Cystoscopy

# 4

Jungyo Suh

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## 4.1 Indication

Cystoscopy is a useful tool for the diagnosis of bladder tumor, but it is also an invasive procedure; thus proper indication for application is essential. About 90% of bladder cancer patients show hematuria; thus the most common indication of cystoscopy is evaluation of gross or microscopic hematuria. Lower urinary tract symptoms (LUTS) are also present in bladder cancer patients, especially carcinoma in situ (CIS) related with storage symptoms. In specific situations with suspicious CIS patient, perform bladder random biopsy through cystoscopic examination. Cystoscopy can also be used for upper tract evaluation by obtaining ureteral cytology and retrograde urethrography.

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## 4.2 Instrument

White light cystoscopy has many limitations; however, it is still a standard tool for diagnosis and surveillance of bladder cancer. Rod-lens optical system-based rigid cystoscopy and fiber-optic flexible cystoscopy each have its merits and faults. Rigid cystoscopy has better visualization, larger working channel, and improved irrigation flow and is easy to handle than flexible cystoscopy. However, rigid cystoscopy has more patient discomfort, especially in male patients, harder inspection of bladder neck and anterior wall, and limited patient positioning.

Rigid cystoscopy needs a sheath, obturator, bridge, and telescope. The lumen of sheath is used for telescope, working instruments, and space for irrigation fluid. Endoscopic instrument size is expressed by the French (Fr) scale which refers to the outer circumference in millimeters. Cystoscopy for pediatric use generally ranges 8–12 Fr and for adult ranges 16–25 Fr. Obturator provides smooth and blunt surface by inserting it to working sheath. Telescope is attached with working sheath by bridge, after removal of obturator. Bridge has one of two working channels, which is used for inserting endoscopic instruments like forceps. Telescopes divide different angle tips to enhance views of specific site of organs. Zero-degree angle provides good orientation and undistorted visual field, so it is commonly used for urethroscopy. Twelve-degree telescope can also be used for urethroscopy. Telescope with 30° lens provides excellent visualization in bladder trigone, dome, and posterior wall however limited visualization in anterior wall and dome. Telescope with 70° lens has advantages in bladder anterior wall and dome visualization; however it is difficult to use for urethroscopy. A 120° lens is used for inspection of bladder neck lesion (Fig. 4.1).

Flexible cystoscopy has internal channel of irrigation and working instruments. Currently available flexible cystoscopy's external sheath diameter is around 16 Fr size for adult. Diameter of flexible cystoscopy is smaller than rigid cystoscopy and less painful; thus many clinicians use it for male patients. The tip of scope provides up to 220° deflection; it can show whole bladder site easily.

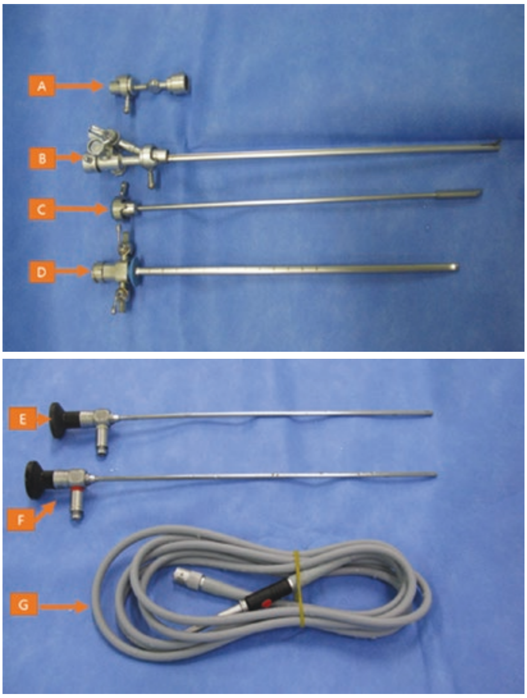

**Fig. 4.1** Instrument for white light cystoscopy examination. (**a**) Telescope bridge or short bridge for connecting telescope to obturator sheath. (**b**) Working element is also called as long bridge. Long bridge also connects telescope and obturator sheath, but it can allow insertion of working element such as foreign body forceps. (**c**) Obturator is inserted in obturator sheath and provides atraumatic access at the time of insertion. (**d**) Obturator sheath has water input channel for bladder filling. (**e**, **f**) Telescope has variable view angles, and operator should select proper instrument for specific situation. (**g**) Light cable for delivering light energy from external light source

## 4.3 Procedure

Cystoscopy (cystourethroscopy), which is used to directly visualize bladder and urethral mucosa, is the most important tool for diagnosis and surveillance of bladder cancer. For obtain best performance of cystoscopy, in full examination of bladder and not miss suspicious lesion is essential.

### 4.3.1 Preparation

If patient is suspicious for urinary tract infection, cystoscopy should be delayed because manipulation of instrument during examination can aggravate infection. Routine administration of antimicrobial prophylaxis is not recommended because it has no benefit for low-risk patients.

The patient should take dorsal lithotomy position for rigid cystourethroscopy. If patient cannot take lithotomy position due to physical deformity or other cause, flexible cystoscopy is the best choice because it is more unconstrained for patient position.

### 4.3.2 Anesthesia

General anesthesia is not recommended for cystoscopy. Local anesthesia with lubricant is useful before cystoscopic examination with rigid endoscope in male patient. Combination of water-soluble lubricant and local anesthesia (e.g., 2% lidocaine) or commercial lidocaine gel is commonly used for anesthesia. For proper anesthesia, urethral clamp is used to keep local anesthetic gel to intraurethral lumen.

There are some studies about pain caused by lidocaine gel administration. Ho et al. [1] report that discomfort during anesthetic gel administration is higher than plain lubricant. The result of this prospective, double-blinded study throws a doubt about pros and cons of local anesthesia. Thompson et al. [2] reported cooling lidocaine gel (4 °C) significantly reduced delivery discomfort than 22 °C and 44 °C. However, these studies have limitation of short instillation time; each was 2 s and 3 s.

Optimal exposure time of administration is still a controversy issue. Some studies agreed that at least 10 min exposure is required to develop full anesthetic efficacy [3]. However, another study shows that there is no difference between immediate and delayed manipulation in flexible cystoscopy [4].

The benefit of local anesthesia before rigid cystoscopy in male population has scientific evidence. Goldfinger et al. [5] report that 30 mL of lidocaine gel to intraurethral administration and left to dwelling 20min significantly reduce mechanical manipulation pain of cystoscopy but not in female. Many randomized studies cannot find merit of dwelling local anesthetic gel before flexible cystoscopy [3, 6–8].

### 4.3.3 Recommendation for Prophylactic Antibiotics

Prophylactic antibiotic administration to prevent urinary tract infection in simple cystoscopy is not recommended. Recent meta-analysis results founded moderate evidence of not recommended antibiotic prophylaxis to prevent UTI and asymptomatic bacteriuria in patients undergoing cystoscopy [9]. Antibiotic prophylaxis is not reduced acute UTI and asymptomatic bacteriuria in patient after flexible cystoscopy [10–12]. If patients have high-risk factor of urinary tract infection, standard antibiotic prophylaxis should be needed (Table 4.1).

### 4.3.4 Bladder Inspection

For inspection of whole bladder without anything missing, systematic approach with checklist is useful. Operator should check up the urethra at the time of insertion with 0° or 12° angled telescope,

**Table 4.1** There are some local and systemic factors that increase risk of post-procedure infections after cystoscopy examination

| Factors that increase the risk of developing infection |
|---|
| Advanced age |
| Anatomical anomalies |
| Poor nutritional status |
| Smoking |
| Chronic steroid use |
| Immunodeficiency |
| Chronic indwelling hardware |
| Infected endogenous and/or exogenous material |
| Distant coexistent infection |
| Prolonged hospitalization |

Copyright from Springer-Nature Publisher [13] finding urethral abnormalities and benign prostatic hyperplasia (BPH) in male. In the male cystourethroscopy insertion, grasp the glans and stretch at 90° angle to the abdominal wall during exploration of penile and bulbous urethra. If visual field is narrow by swallowed urethra, give more pressure on irrigation fluid makes distending the urethral lumen and obtain clear visualization. Membranous urethra is characterized by transversely located striated muscle and normally contacted by both mucosae. Verumontanum is positioned posterior at the right after membranous urethra, which placed distal portion of prostatic urethra. In the prostatic urethra, the operation evaluated lateral lobe, kissing sign, median lobe elevation, and prostatic length for BPH. Sometimes, additional anterior angulation is for elevating the endoscope over the elevated bladder neck or BPH patients.

When the sheath is placed in the bladder properly, operator changes 30° or 70° angled telescope which provides excellent visualization of bladder. In bladder trigone area, operator should find both ureteral orifice and efflux of urine from ureter. No urine efflux in single site of ureteral orifice or jetting of hematuria can be a sign of ureteral or renal lesion; in that case, you should consider upper tract evaluation. If there are no urine effluxes in both sides of the orifice, you should consider prerenal cause. After inspection of bladder trigone, sequential evaluation of bladder posterior, left and right wall. Anterior wall and dome site are sometimes not easily visible, and then external compression of bladder is a useful technique. Telescope with 70° angle should provide excellent visualization for bladder anterior and dome, so changing telescope lens in patients with difficult views of those sites of the bladder should be necessary.

## 4.4 Typical Findings of Bladder Cancer

Detection of bladder malignant lesion by cystoscopy is based on shape and color of bladder lesion. About 90% of bladder cancer consists of urothelial carcinoma, and two-thirds of them show papillary growth; thus most of malignant lesions of bladder present typical shape. Thus, do not miss the typical lesion of bladder tumor which is crucial in performing cystoscopy.

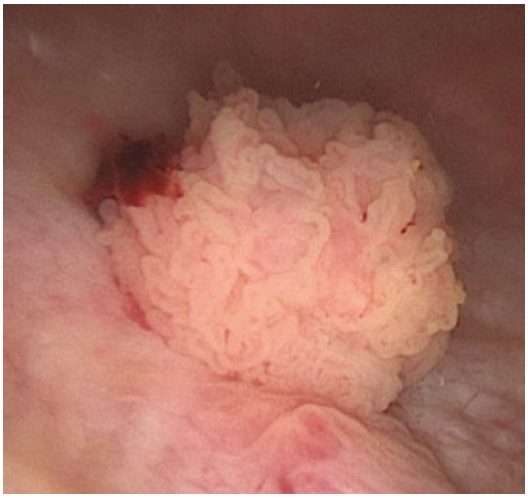

**Fig. 4.2** Typical papillary shape of urothelial carcinoma in bladder

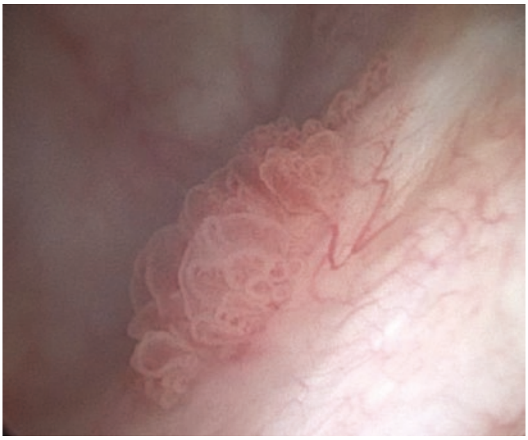

**Fig. 4.3** Some papillary urothelial carcinoma shows sessile appearance. This patent is diagnosed with papillary high-grade urothelial carcinoma without stromal invasion

Typical shape of papillary urothelial carcinoma has a stem and broccoli- or cauliflower-looking head (Fig. 4.2). Because of active angiogenesis of cancer, many vessels are visible at the head of tumor with or without bleeding. Size varies by patients, and depth of invasion is not correlated with tumor size. Some of papillary urothelial carcinoma does not make stalk and shows sessile growth (Fig. 4.3). Round elevation of uroepithe-

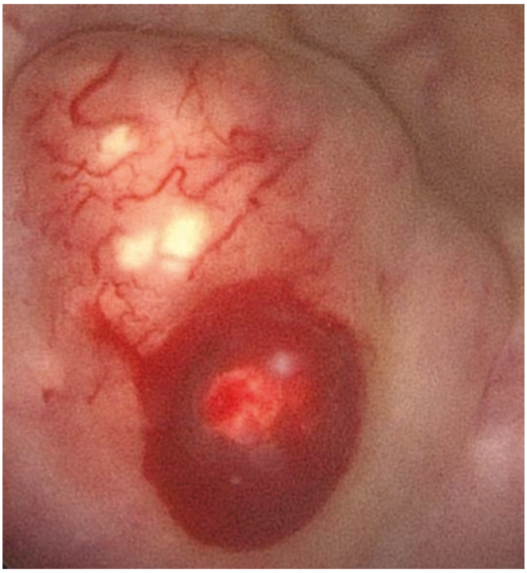

**Fig. 4.4** Solid mass-like elevation of urothelial lining has possible positive findings for urothelial carcinoma. This patient is diagnosed with muscle invasive bladder cancer

lium with solid-looking appearance is also an abnormal finding that could be suspected for urothelial carcinoma (Fig. 4.4). In progress disease, mass is combined with necrotic lesion or blood clot. Standard white light cystoscopy (WLC) has high specificity and sensitivity for detecting papillary bladder cancer; however, tumor appearance alone cannot predict invasiveness or grade [14].

Carcinoma in situ (CIS) of urothelial carcinoma has flat, high-grade, and noninvasive but highly aggressive characteristic (Fig. 4.5). CIS lesion presents flat erythematous lesion and is not easy to find in standard WLC. To overcome low yield of detecting CIS in WLC, enhanced endoscopic techniques like photodynamic detection (PDD) or narrowband imaging cystoscopies (NBI) are upcoming.

Some benign findings are frequently encountered during cystoscopic examination. Inverted papilloma typically maintaining smooth urothelium with small pedunculate or sessile appearance. Cystitis cystica and glandularis are the most commonly founded benign lesions, especially in patients maintaining urologic catheters or intermittent catheterization. Cystitis typically shows cystic change of urothelium and has a cobblestone appearance.

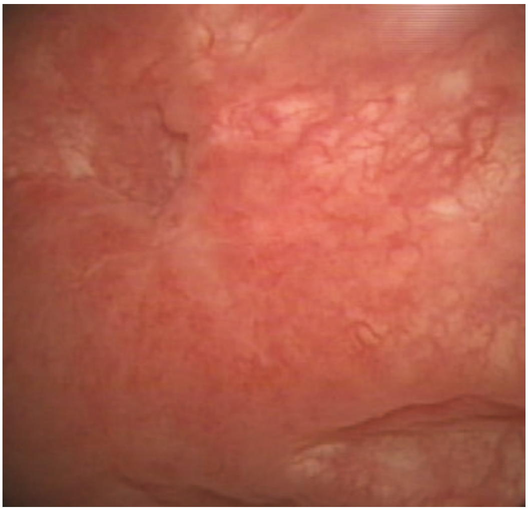

**Fig. 4.5** Detection of carcinoma in situ (CIS) lesion by conventional white light cystoscopy is challenging. Clinical suspicion is essential, and sometimes bladder random biopsy or investigation of whole urinary system, from renal pelvis to urethra, is needed

## 4.5 Benefits for Using Flexible Cystoscopy in Male Patient

Application of glass fiber to endoscopy leads to development of flexible cystoscopy. Because of thin and elastic glass fiber, flexible scope has a small external sheath diameter and is bendable up to 220°. This characteristic makes it an advantage to use flexible cystoscopy in a specific situation.

The male urethra has a long and curvy course; cystoscopic procedure makes pain and intraluminal trauma easily. Flexible cystoscopy has smaller external sheath diameter and can be bendable with urethra course; it can make the patient more comfortable. It is also useful in patient with urethral stricture or severe BPH.

## 4.6 Advance Cystoscopy Technique (NBI/PDD/OCT)

Since Maximilian Nitze (1848–1906) introduced first contemporary cystoscopy, white light cystoscopy (WLC) is constantly innovated. Advancement of digital sensor, such as charge-coupled device (CCD) and complementary metal-oxide semiconductor (CMOS) and high-definition imaging technique, guarantees high diagnostic accuracy of papillary bladder cancer. However, current white light cystoscopy has limited diagnostic yield on carcinoma in situ and is only 23–68% [15], and failure to detect CIS result significantly impacts on patient outcome [16]. Evaluation of residual tumor on the time of transurethral resection of bladder tumor (TURBT) and detection of tiny malignant lesions are also challenging. Novel-enhanced imaging modality that is adjuvant to standard cystoscopy is promising to overcome these issues.

### 4.6.1 Narrowband Imaging (NBI)

Narrowband imaging uses different penetrating depth between two light wavelengths of 415 nm (blue) and 540 nm (green) [17] (Fig. 4.6). The blue light, which has shorter wavelength (415 nm), penetrates only the superficial mucosal layer and is absorbed by binding with hemoglobin in blood vessels. The green light penetrates a deeper layer than blue light and then absorbed by deep or submucosal layer of blood vessels. The result of these process shows vascular network of superficial (brown) and deep (green) layer (Fig. 4.7).

Since Bryan et al. [19] first report application of NBI in flexible cystoscopy, several studies focus on advantage of NBI with WLC to detect bladder cancer compared to WLC alone. Li et al. [20] conducted meta-analysis of seven prospective studies of non-muscle-invasive bladder cancer (NMIBC) and founded that NBI detects additional 24% of papillary tumor and 28% of CIS than that of WLC. Zheng et al. [17] performed another meta-analysis of eight studies to compare diagnostic effectiveness of NBI and WLC. This study discovered that NBI was a more effective diagnostic method to find abnormal lesion, especially in CIS lesion, with higher diagnostic odds ratio than WLC (185.32 vs. 42.931 in papillary tumor, 0.927 vs. 0.768 in CIS, respectively).

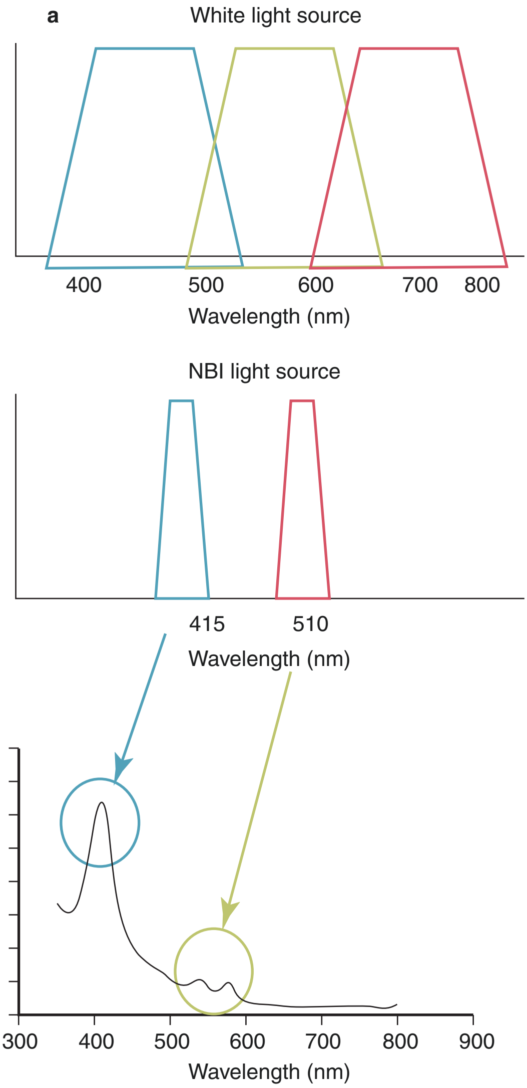

**Fig. 4.6** Narrowband image (NBI) uses specific wavelength of light to enhance vascular structure of urothelial carcinoma. Copyright from Springer-Nature Publisher [18]

The evaluation response of bacillus Calmette-Guerin (BCG) to treat CIS is often challenging because of BCG-induced inflammatory response. NBI is a promising tool for overcoming this difficult issue. Preliminary cohort study to find diagnostic effect of NBI compared with WLC with urine cytology is performed by Herr [21]. This study containing 61 patients with suspicious lesion in WLC and 22 (36%) patients had

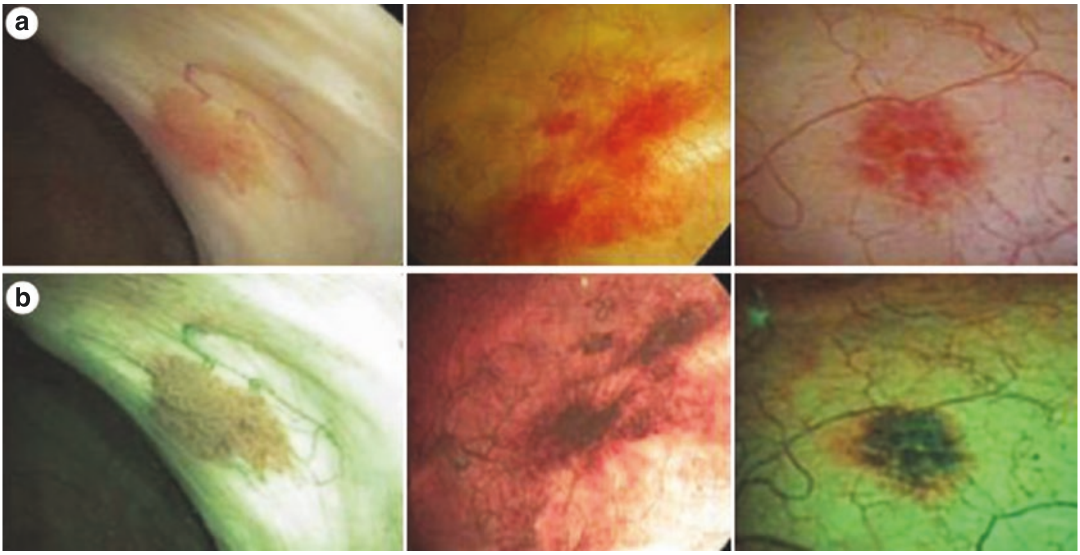

**Fig. 4.7** Matched images of white light cystoscopy (WLC, **a**) and narrowband imaging technique (NBI, **b**). Copyright from Springer-Nature Publisher [18]

residual tumor in 3 months after BCG therapy. NBI correctly founded 21 patients and loss one patient with CIS, but ten patients had unnecessary procedure. Sensitivity and negative predictive value were significantly higher in NBI than cytology (95% vs. 59% and 97% vs. 77%). Specificity and positive predictive value of NBI were higher than cytology but not statistically significant (78% vs. 77%, 68% vs. 59%).

Therapeutic application of NBI added with TUR procedure is another promising field. A prospective study of 135 patients performed by Kobatake [22] reported that NBI-TUR group has significantly higher sensitivity (95.0% vs. 70.0%) and negative predictive value (97.1% vs. 86.8%) than WLC-TUR group. Moreover, NBI-TUR group shows significantly lower 1-year recurrence rate than WLC-TUR group (21.1% vs. 39.7%).

Application of NBI is very easily with just put and off wavelength screening filter on cystoscopy. Current available NBI system support easily switches to WLC and provides more detection of tumors without increase of risk or cost to patients than another advanced cystoscopy technique.

### 4.6.2 Photodynamic Diagnosis

Photodynamic diagnosis is one of another macroscopic imaging modality to enhance diagnostic accuracy of conventional WLC. Photodynamic diagnosis (PDD) requires preoperative intravesical instillation of photosensitive contrast agent. Instilled fluorophore mostly uses 5-aminolevulinic acid (5-ALA) or hexaminolevulinate (HAL) absorbed to urothelium and excessively accumulates on cancer cell and fluoresces red light under blue light source (375–550 nm wavelength). This is why PDD is called blue light cystoscopy (Fig. 4.8).

5-ALA and HAL are currently available protoporphyrin analogues for PDD for clinical use in the European Union and the United States. HAL was reported with greater stability and fluorescence intensity and higher fat solubility than 5-ALA.

Most studies agreed with PDD has significantly higher diagnostic rate than WLC in small Ta lesion and CIS lesion [24–27]. In a meta-analysis conducted by Burger et al. [25], it shows that HAL-PDD has significantly higher detection rate on Ta (14.7%) and CIS (40.8%)

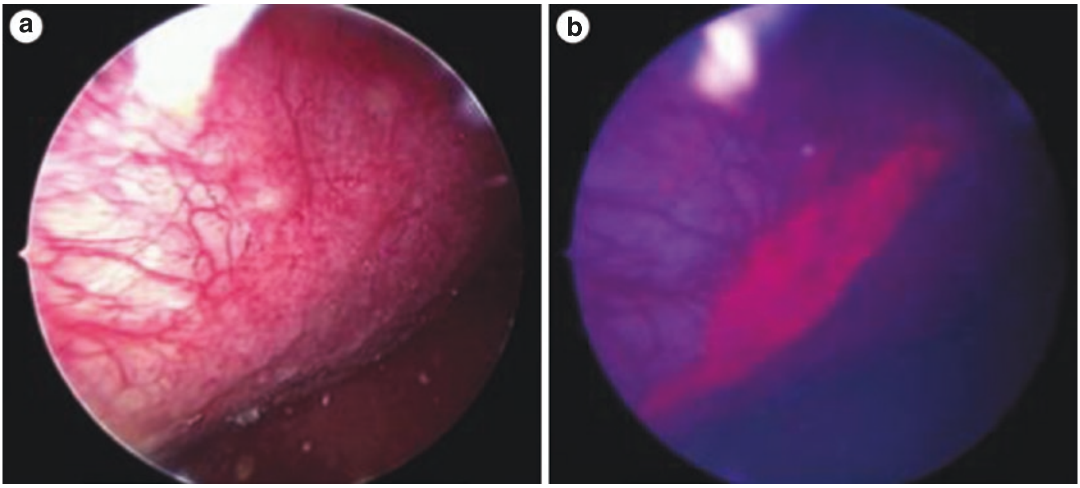

**Fig. 4.8** HAL–BLC can detect recurrent NMIBC. A 77-year-old woman with a longstanding history of NMIBC—she had undergone office fulguration of ten tumors over 5 years, all of which were pathologically confirmed as low-grade Ta lesions—was referred to our institution. She received five instillations of BCG and was unable to complete the sixth instillation because of severe irritative lower urinary tract symptoms. After 6 months she received three instillations of half-strength BCG. Three months later, she again experienced recurrence and sought a second opinion. She had HAL–BLC and TURBT under anesthesia in the operating room. (**a**) A small area of potential tumor was identified on WLC. (**b**) HAL–BLC revealed extensive (red) fluorescence corresponding to a large lesion. On pathological analysis, the lesion was found to be CIS, which might have been in existence for some time. Abbreviations: *BLC* blue light cystoscopy, *CIS* carcinoma in situ, *HAL* hexaminolevulinate, *NMIBC* non-muscle-invasive bladder cancer, *TURBT* transurethral resection of the bladder tumor, *WLC* white light cystoscopy. Copyright from Springer-Nature Publisher [23]

than WLC. CIS that is only founded in HAL-PDD was also significant both in primary or recurrent tumor (28.0% and 25.0%). Recurrence up to 1-year follow-up period was significantly lower in HAL-PDD (34.5%) than WLC (45.4%). Rink et al. [27] performed systematic review of 44 studies and founded that sensitivity for PDD ranged 76% to 97% which was higher than sensitivity of WLC (ranged 46–80%).

PDD-TUR can reduce the risk of recurrence by detection and reduction of residual tumor during operation. A systematic review of Rink et al. [27] reveals PDD-guided TUR group shows lower residual tumor rate (range 4.5–32.7%) than WLC group (25.2–53.1%). There was some conflicting result; however most of the studies agreed with recurrence-free survival which was lower in PDD group than WLC group.

PDD is the most anticipating technique for enhancing detection of small papillary tumor and CIS adding to WLC. Guidelines from the European Urology Association (EAU) and International Consultation on Urological Disease (ICUD) already recommend to using PDD, and American Urological Association (AUA) also supports this recommendation recently.

### 4.6.3 Microscopic Imaging

Confocal laser endomicroscopy (CLE) uses low-power laser (488 nm) and selectively obtains scattered light of in-focus plane by pinpoint laser scanning unit [28]. High sensitivity to fluorescence of CLE provides greater imaging contrast than another microscopic endoscopic imaging technique. CLE provides real-time, in vivo histological imaging also known as “virtual biopsy” with high resolution (2–5 μm) and high penetration depth (2–5 μm); thus this novel technique has potential benefit for identifying histologic grade information of UCC during cystoscopic examination [29, 30].

Since this novel technology was introduced in 2004 [31], CLE currently approved its clinical use only in gastrointestinal tract and respiratory tract. Application in urothelial carcinoma is still experimental; however, Son et al. [29] successfully visualized the normal bladder urothelium/lamina propria and classified normal urothelium, low-grade, high-grade UCC by CLE in 2009. Developed CLE probe is as small as 1.4 mm diameter; thus it can pass through the working channel of rigid cystoscope. However, this technique obtained small field image by direct contact of tissue, through probe or CLE-integrated endoscope tip; CLE cannot increase detection rate of UCC or others like NBI or PDD. Further studies for overcoming limitation and determining suitability of CLE in UCC are required.

Optical coherence tomography (OCT) is another type of microscopic endoscopy on experimental stage. OCT provides high-resolution cross-sectional image (10–20 μm) with 2–3 mm depth of image [32]. This novel technique similar with imaging obtains mechanism of ultrasonography, but OCT uses near-infrared light instead of ultrasound [33]. OCT can differentiate normal urothelium and urothelial carcinoma with their infiltration status; however, it cannot identify tumor grade [34].

After first demonstration of OCT in 1991 [35], it consistently improved in the past decades. Clinical use of OCT weighted on diagnosis of retinal disease in ophthalmology and cardiology field, and recently it was applied in urology field. Manyak et al. [36] successfully demonstrated in vivo use of OCT to detect UCC of bladder with 100% of sensitivity and 89% of specificity. Lerner et al. [37] also reported high accuracy of OCT combined WLC, with a sensitivity and specificity of 90% and 89% in mucosal lesion and 100% and 90% in muscle-invasive lesion.

Mechanism of cancer detection by OCT is based on intercellular disruption by cancer cell; thus false-positive result can be made by benign lesion, which makes structural anomalies such as inflammation, scarring, and ulceration [16]. This limitation was expected to be overcome by combination with PDD or NBI. A prospective study pointed out that combination of HAL-PDD with OCT increases specificity and reduces false-positive result, by 79.6–97.9% in specificity [38]. Another limitation of OCT is small field of view and requires some training period to interpretation of OCT images.

### 4.6.4 Other Upcoming Imaging Technologies

Raman spectroscopy (RS) and molecular imaging are another potential imaging modalities to enhance bladder cancer diagnosis by cystoscopy.

Raman spectroscopy uses Raman scattering (inelastic scattering) of protons, which is gain or loss of energy by interaction with intermolecular bonds. Raman scattering induced by all types of monochrome light source mostly uses infrared light in urologic endoscopy. There is ex vivo report of successfully identifying UCC grade and stage in 75 bladder cancer tissue samples [39]. In vivo study shows promising result with 85% sensitivity and 79% specificity [40]. However, Raman spectroscopy has limitation of weak signal, fluorescence interferences, and small view area [41].

Molecular imaging uses intravesical administration of fluorescence-labelled molecules, such as antibodies, peptides, or another material. This molecule is selectively attached to urothelial carcinoma of bladder, and a physician could detect this suspicious lesion. Ex vivo result using CD47 antibody-coated nanoparticle shows 82.9% of sensitivity and 90.5% of specificity [42]. This novel technique has potential benefit for combination of diagnosis and targeted therapy using CD47 antibody.

## 4.7 Follow-Up

Because of high recurrence rate, risk classification, providing adequate surveillance, is one of the most important parts of bladder cancer management. NCCN, EAU, and AUA guidelines use tumor size, grade, number, and specific pathologic features for assessing recurrence and progression risk [43–45]. EAU guideline uses

EORTC risk table; only the primary case is possibly included in low-risk group, if, in recurrent case, minimal risk is intermediate group. AUA guideline [45] uses recurrence interval as risk-stratification factor; if patient recurred within 1-year interval, minimal-risk group is intermediate. PUNLMP is considered low-risk group only in AUA. Concomitant carcinoma in situ, lymphovascular invasion, and any variant histology are considered as high-risk groups in AUA, but EAU only agreed with concomitant CIS.

Surveillance protocol is based on cystoscopic examination and followed by risk group. EAU and AUA guidelines agreed with at least 3-month follow-up after initial treatment, with any risk group [44, 45]. Low-risk group needs additional 6–9-month follow-up after first follow-up cystoscopy and continued annually at least 5-year follow-up. Intermediate- and high-risk groups need cystoscopy and urine cytology with lifetime follow-up periods.

Upper tract evaluation is not always recommended. EAU guideline suggests annual upper tract evaluation only in high-risk group. AUA guideline suggests upper tract evaluation for intermediate- and high-risk group, but not in low-risk group.

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# Urine Cytology and Emerging Biomarkers

# 5

Jungyo Suh

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## 5.1 Urine Cytology

Urine cytology is a pathologic diagnosis of cellular smear from patient urine. Since Dr. Papanicolaou suggests microscopic evaluation of urine exfoliated cells, urine cytology still takes the main position for diagnosis of bladder cancer. Conventional urine cytology has limited accuracy caused by examiner dependency, cellular yields, and inflammatory lesion [1]. Liquid-based cytology (LBC) developed in the 1990s provides a more automated and standardized processing with reduced background obscuring cells like inflammatory cells and red blood cells. This advancement resolved one of the most limitations of conventional cytology, cellular yield; however diagnosis is still based on morphological assessment; thus operator dependency is still in position of major limitation. Specificity of urine cytology is high enough; however, sensitivity for low-grade lesion and CIS was too low as 16% [2, 3].

### 5.1.1 Normal Findings in Cytology

Urinary cytology is used for diagnosis of bladder cancer by morphological feature. Normal urothelial cells consisted superficial “umbrella cells,” which are generally flat, polygonal shaped with abundant cytoplasm, and deep transitional cells. Columnar cell from Von Brunn’s nests is often

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found in urine with cystitis cystica. Renal epithelium, glomerular, or tubular cells can sometimes be detected in urine [4].

Infectious lesion is also considered as non-tumoral pathology. Enlarged nuclear with high nuclear to cytoplasmic (N/C) ratio and basophilic intranuclear lesion is typical in polyomavirus infection. HSV and CMV infections are also found in urine sediments with typical pathology. HSV infection is found with multinucleated, “ground-glass” nuclei and large eosinophilic intranuclear inclusion surrounded by halo. CMV infection shows also large nuclear with cyanophilic inclusion surrounded by halo.

### 5.1.2 Malignant Findings in Cytology

The majority of malignancies that occurred in the bladder were urothelial carcinoma. According to WHO/ISUP classification, cytologic diagnosis of bladder urothelial carcinoma is classified by two groups: low-grade and high-grade lesions. Another less common malignancy of the bladder can be found in urine cytology, including squamous cell carcinoma and adenocarcinoma, but diagnostic accuracy is much lower than urothelial cell carcinoma.

Diagnosis of low-grade urothelial carcinoma by urine cytology is very difficult. Typical cytologic features of low-grade tumor show grooved and small nucleoli, increased N/C ratio with enlarged cytoplasm than normal urothelium, and papillary structure with fibrovascular cores. Papillary cluster has diagnostic power only in voided urine specimen because instillation of urinary instrument can make pseudo-lesion.

High-grade urothelial carcinoma is defined with moderate to marked cellular atypia, high N/C ratio, large hyperchromatic nucleoli, coarse chromatin, and large numbers of exfoliated cells. Differential diagnosis of carcinoma in situ (CIS) and high-grade UCC is not easy. Necrotic debris in background prefer invasion, thus more favorable sign of CIS lesion.

Diagnosis of non-urothelial malignancy of the bladder is challenging. Squamous cell carcinoma shows keratinizing neoplastic cell with atypical shape and is sometimes observed with squamous pearl. Adenocarcinoma shows vacuolizing group of atypical cells and “signet ring” cells [4].

### 5.1.3 Routine Evaluation of Urine Cytology in Hematuria Patients

Urine cytology is the most widely accepted urinary biomarker; however, it is limited with respect to sensitivity and has issues related to inter- and intra-observer variability. There is early report of routine evaluation of urine cytology that is not recommended in initial hematuria [5]. In the manner of cost-effectiveness, some physician considered routine evaluation of urine cytology for detecting recurrence in prior NMIBC patients is unnecessary [6].

Current guideline recommended urine cytology as ancillary diagnostic method. Most of the AUA guidelines make no recommendation regarding urine cytology in the primary assessment but advocate its use in the surveillance of intermediate- and high-risk patients. Conversely, the EAU and NCCN guidelines recommend the use of urine cytology as an adjunct to cystoscopy at primary assessment and in the surveillance of high-risk tumors. NICE guidelines are the least specific, stating that it should be offered at the time of TURBT (or alternatively, enhanced cystoscopic visualization or another urinary biomarker).

### 5.1.4 Washing Cytology vs. Voided Urine Cytology

There are two available methods to obtain cytology specimen of urine: voided urine or bladder washing. Current guideline does not decide which one is the superior urine collection method for cytologic diagnosis. In the comparative research of 1458 patients visiting outpatient clinic, cytologic result has no relevant difference between voided urine and bladder washing [7]. There are some reports for superiority of washing cytology than voided urine to diagnosis of low-grade malignancies, but this still has no consensus [8].

### 5.1.5 The Paris System for Reporting Urinary Cytology (PSRUC)

Not only technical difficulty of preparation and histologic review but also interpretation of report is another major problem of urine cytology. The communication gap between physician and pathologist is chronic problem [9] and not easy to fix. First attempt to reduce misinterpretation of pathologic report by standardized reporting terminology was not successful [10, 11]. The Paris system born to overcome communication problem by both pathologist and urologist developed novel reporting strategies [11].

TSRUC reporting system focused on detecting and reporting high-grade urothelial carcinoma, because of its clinical importance. About 70% of bladder urothelial carcinoma presented with non-muscle invasive bladder cancer (NMIBC) and most of them diagnosed as low-grade urothelial carcinoma. Although low-grade cancer is easily controlled by transurethral resection, patients who progressed to high-grade NMIBC or muscle invasive bladder cancer show poor prognosis.

Previous cytologic reporting systems frequently used “suspicious,” “indeterminate,” or “atypical,” when pathologist could not clearly rule out malignant lesion. However, these terms felt more severe to clinician, regardless of clinical inspection. To remove these linguistic gaps, PSRUC provides seven categories for report and diagnostic algorithm to standardization (Table 5.1, Fig. 5.1).

Unsatisfactory cytology means there are only ambiguous urothelial cells in urine, because of lubricants or inflammation. If the sample has only single cell with favorable malignancy, it is considered as an adequate sample. Most of the specimens are relevant to negative for high-grade urothelial carcinoma (NHGUC) categories. Mild-level cellular atypia with predisposing clinical condition that can makes cellular atypia and all benign changes, such as viral infection, classified as NHGUC. Atypical urothelial cell (AUC) is clinically gray zone and major target of PSRUC try to reduce. Thus, strict conditions required one of the major criteria and another one of the minor criteria. For minimizing undiagnosed lesion, PSRUC recommend ancillary test, like FISH or NMP22 test, to obtain additional information in AUC class. Suspicious for high-grade urothelial carcinoma (SHGUC) contained severe cellular atypia but found only a few amounts in specimen. Clinicians should pay more attention in patients with this category than AUC category, because of higher chance of malignancy. The concept of high-grade urothelial carcinoma (HGUC) is unchanged since Dr. Papanicolaou demonstrates from urine sediments. By PSRUC, the diagnosis of HGUC requires morphologic criteria, with two major aspects (N/C ratio, nuclear hyperchromasia) and one minor aspect, and quantitative criteria (more than 5–10 suspicious cells).

**Table 5.1** Seven categories of the Paris System for Reporting Urinary Cytology (Copyright from Wolters Kluwer Health, Inc. (Publisher)) [11]

| Category |
|---|
| Inadequate/less than optimal adequacy |
| Negative for high-grade urothelial carcinoma (NHGUC) |
| Atypical urothelial cells (AUCs) |
| Low-grade urothelial neoplasm (LGUN) |
| Suspicious for high-grade urothelial carcinoma (SHGUC) |
| High-grade urothelial carcinoma (HGUC) |
| Other malignancies primary and metastatic |

PSRUC cannot suggest morphological criteria appropriate for diagnosis of low-grade urothelial carcinoma (LGUC). The presence of fibroblastic core can present any low-grade urothelial lesion including papillary urothelial neoplasm of low malignant potential (PUNLMP) and papilloma. Thus, this category is separated from other categories using exclusive diagnosis from NHGUC by cystoscopy, radiology, and clinical impression. PSRUC system also classified another malignancy that occurred in bladder cancer. This other malignancy category

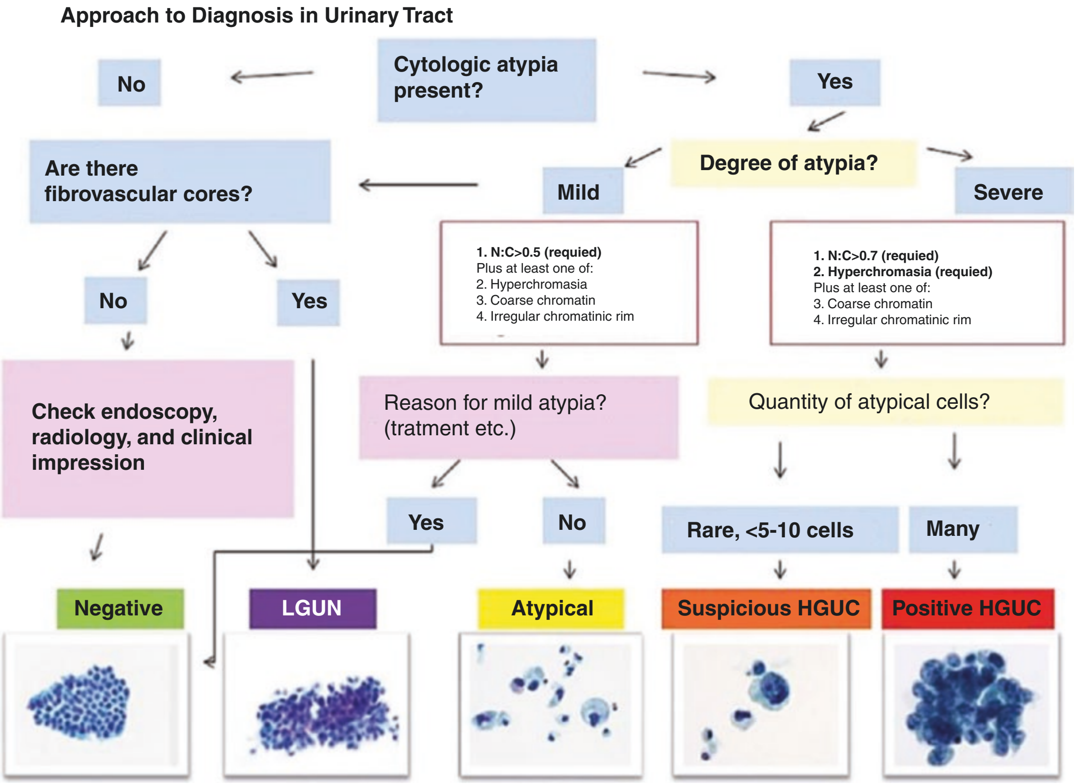
Approach to Diagnosis in Urinary Tract
Cytologic atypia present?
No
Yes
Are there fibrovascular cores?
Degree of atypia?
Mild
Severe
No
Yes
1. N:C>0.5 (requied)
Plus at least one of:
2. Hyperchromasia
3. Coarse chromatin
4. Irregular chromatinic rim
1. N:C>0.7 (requied)
2. Hyperchromasia (requied)
Plus at least one of:
3. Coarse chromatin
4. Irregular chromatinic rim
Check endoscopy, radiology, and clinical impression
Reason for mild atypia? (tratment etc.)
Quantity of atypical cells?
Yes
No
Rare, <5-10 cells
Many
Negative
LGUN
Atypical
Suspicious HGUC
Positive HGUC

**Fig. 5.1** Diagnostic algorithm of the Paris System for Reporting Urinary Cytology (Copyright from Wolters Kluwer Health, Inc. (Publisher)) [11]

contained non-urothelial origin primary bladder cancer (squamous cell carcinoma, adenocarcinoma, and small cell carcinoma) and metastatic malignancies.

#### 5.1.5.1 Pros and Cons of the Paris System for Reporting Urinary Cytology

The Paris System for Reporting Urinary Cytology (PSRUC) shows improvement for several aspects of urine cytology diagnosis [12]. The most important achievement of PSRUC is reducing the clinical "gray zone," atypical cells. Hassan et al. show [12] reduction of AUCs after application of PSRUC than original system, from 39% to 26%. PSRUC provide more clear differences between each category for prediction of HGUC in surgical specimen [12]. Original system has no clear differences between SHGUC with HGUC and NHGUC with AUCs. Categorical differences between positive predictive values of HGUC were increased in PSRUC, and this attribute provides more information in clinical decision-making. HGUC class in PSRUC has similar detecting power of high-grade tumor as original system, without any decrement of diagnosis numbers. Cowan et al. [13] reported about 25% of HGUC specimen in classic classification system downgraded under PSRUC; however, 17–21% of AUC specimen upgraded to HGUC. Upgraded specimen to HGUC from AUCs has rare malignant cell with lack of cellular enlargement, thus missed diagnosis under original system. Finally, PSRUC system provides more sensitivity to correlation with surgical diagnosis than original cytology, especially in lower urinary tract and high-grade tumor [12, 14].

Although PSRUC provides superior result by reduction of AUCs and higher risk stratification than the previous classification system, there are some limitations. PSRUC uses strict morphological criteria of nuclear border of urothelial cells;

specimen degeneration and sampling methods affect its diagnosis [13, 15]. In degenerated specimen of HGUC, nuclei shrinkage and vacuolated cytoplasm can be an alteration of diagnosis by decreased N/C ratio. Some of well-preserved specimen shows round nuclear border, and some of degenerated specimen makes difficult the diagnosis of chromatin pattern because of higher hyperchromasia that leads to less elevated N/C ratio [13].

Another limitation of PSRUC is related with sampling problem. Instrumented sampling can affect result of nuclear border irregularity (78% in voided urine vs. 89% in washing and catheterized urine) [13] and makes artifacts, such as tissue fragmentation [8]. For this reason instrumented urine and bladder washing cytology can make shifting diagnosis to AUC from LGUC category [8]. Owing to PSRUC using strict morphological criteria for classifying UCC grading, sampling variation must be considered before diagnosis.

## 5.2 Biomarker

### 5.2.1 Currently Available Biomarkers

Many of the novel bladder cancer biomarkers are developed within several decades, for early detection and recurrent diagnosis. Several biomarkers are approved by FDA (BTA stat, BTA TRAK, NMP22, ImmunoCyt, and UroVysion) for clinical use with encouraging initial diagnostic performance. However, diagnostic performance in general population is not reproducible; thus none of them replace current gold standard, urine cytology.

NMP22 and BTA test is available with point-of-care test (POCT) form, whereas the others are performed in laboratory. UroVysion and ImmunoCyt detected bladder cancer cells by FISH and ELISA; other tests use detection of soluble urinary biomarker by ELISA. Recent rapid development of next-generation sequencing (NGS) technology promises to use ctDNA (cell-free tumor DNA) and miRNA of bladder cancer as biomarker. Most of biomarkers focused on early detection but ImmunoCyt can applying for follow-up of bladder cancer.

Because of inadequate clinical performance of currently available biomarkers, routine use of these biomarkers is not recommended by any of AUA/EAU/NCCN and NICE guidelines. The AUA guidelines recommend use of biomarker in specific condition, for assessing BCG response or equivocal cytology. The NCCN guidelines recommend use of urinary biomarkers for only in surveillance setting.

### 5.2.2 Urinary Biomarker

#### 5.2.2.1 Nuclear Matrix Protein-22 (NMP22)

Nuclear matrix proteins (NMPs) are structural framework of the nucleus, and these proteins play an important role in DNA mitotic process. NMP22 is specific for the nuclear mitotic protein with proper distribution of chromatids to daughter cells [16]. NMP22 concentration is 25 times higher in bladder cancer cell line than normal bladder urothelium [17] and 5 times higher in bladder cancer patient urine than normal control [18].

The quantitative NMP22 detection is preceded by a two-step sandwich enzyme-linked immunosorbent assay (ELISA). The reference cutoff value of NMP22 had been set to 10 U/mL by the manufacturer. A qualitative NMP22 detection (BladderChek, Alere Scarborough, Inc., Waltham, MA, USA) is based on immunochromatographic assay device using point-of-care test (POCT). Both quantitative and qualitative NMP22 tests are approved by US FDA.

Sensitivity and specificity of quantitative NMP22 vary by studies. Pooled sensitivity of NMP22 ELISA for overall diagnosis was 0.69 (0.62–0.74; 95% CI) by the most recent meta-analysis [19]. Sensitivity of qualitative NMP22 was 0.58 (0.39–0.75; 95% CI) by the same study. NMP22 shows lower sensitivity in recurrent tumor than primary tumor, especially in lower-grade tumor [2]. Patient with recurrent UTI and urinary calculi shows high false-positive rate of both NMP22 tests (33–50%). Because of high false-positive rate, NMP22 could not be used alone but adjuvant with cystoscopy.

#### 5.2.2.2 Bladder Tumor Antigen (BTA)

Bladder tumor antigen (BTA) test targeted complement factor H and complement factor H-related protein in patient's urine specimen [20]. Both quantitative test (*BTA TRAK*, Polymedco Inc., Cortlandt Manor, NY, USA) and qualitative test (*BTA stat*, Polymedco Inc., Cortlandt Manor, NY, USA) are approved by US FDA. BTA TRAK uses sandwich ELISA methods and needs specialized facility, but BTA stat can be performed in POCT (point-of-care test).

Overall sensitivity of BTA TRAK was reported as 65%, diagnosis as 76%, and surveillance as 58% [21]. Overall sensitivity of BTA *stat* was similar to BTA TRAK with 64%, diagnosis 76%, and surveillance 60% [21]. Overall specificity of BTA tests is 77% in qualitative test and 74% in quantitative test [21]. BTA stat demonstrates higher sensitivity with increasing stage and histologic grade [22].

False-positive rate is higher in BTA tests like NMP22. It shows high false-positive rate with patients with benign diseases causing hematuria, such as UTI, urinary calculi, and BPH [16]. Bladder cancer patient with BCG instillation also shows false-positive result in BTA test. Thus, combining it with cystoscopy should be essential for qualifying BTA test results.

#### 5.2.2.3 Urine Protein

Owing to easy accessibility, noninvasive collection, and stability, urine is considered as good body fluid for biomarker study. Bladder cancer has major advantage for urine proteomics and genomics study, because of cancer cell direct contact with urine for a long time [23]. For this reason, protein biomarker discovery in bladder cancer is mainly preceded in urinary sample rather than blood sample.

Various proteomics approaches to identify potential protein biomarkers include gel-based (2DE, DIGE), gel-free (CE-MS, LC-MS/MS), and combined technique (iTRAQ), as well as bioinformatics-based approach [23].

Many proteins are discovered as potential biomarker for bladder cancer; however most of these proteins are not specific to bladder cancer and have low accuracy for diagnosis [23]. The next step for protein biomarker discovery focused to improve the low performance of single biomarker by composing multiple-biomarker panel.

#### 5.2.2.4 Urine MicroRNA

Micro-ribonucleic acids (miRNAs) are short noncoding RNAs and regulate posttranscriptional gene expression. Recent studies show potential usage of miRNA expression profile as cancer classification, early detection, and prediction of disease prognosis [24, 25]. Secretary miRNAs in body fluid have benefit for easy accessibility and high stability than tissue sample [26]. For this reason, urine miRNAs are another potential biomarker for bladder cancer diagnosis.

Recent several studies show potential usability of urinary miRNA as bladder cancer biomarker [27–31]. Pooled sensitivity and specificity of miRNA for diagnosis of urothelial carcinoma of bladder were 0.80 (95% CI: 0.78–0.81) and 0.74 (95% CI: 0.72–0.76) by recent meta-analysis [32]. MiRNA-126, miRNA-200, and miRNA-183 families happen to be the most expected biomarkers for bladder cancer, but further studies are needed to confirm these primitive results [33].

### 5.2.3 Cell-Based Biomarker

#### 5.2.3.1 ImmunoCyt/uCyt

Immunocyt/uCyt+ detect exfoliated urothelial carcinoma cell in urine using fluorescent-labeled monoclonal antibody. More than one of red or green fluorescent light detected in urine specimen considered positive results in these immunocytological assays (Fig. 5.2) [16]. This study is approved by US FDA for diagnosis of bladder cancer.

Recent meta-analysis of seven studies shows better sensitivity with 0.725 (95% CI: 0.683–0.765) than urine cytology (0.566; 95% CI: 0.521–0.611); however specificity was lower than urine cytology [35]. Pooled sensitivity and specificity of combined ImmunoCyt and urine

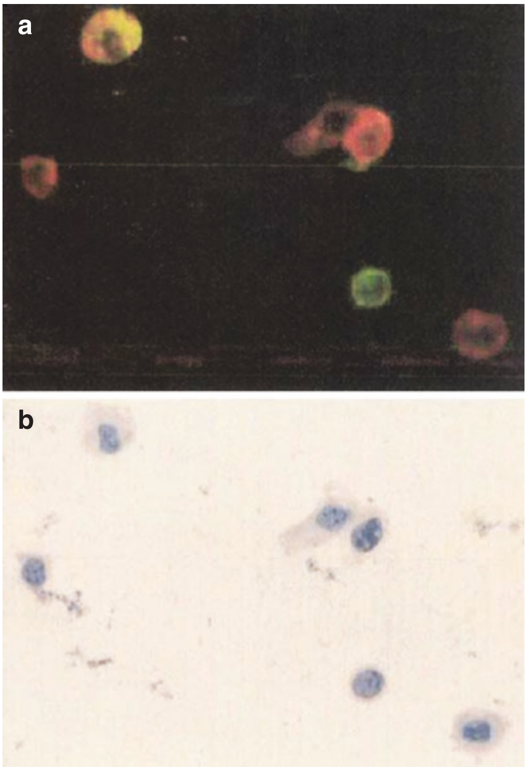

**Fig. 5.2** Presence of atypical urothelial cells as seen by (**a**) immunofluorescence with ImmunoCyt/uCytt (×400, Texas red and fluorescein) and (**b**) light microscopy (×400, modified Papanicolaou stain) (reproduced with permission from DiagnoCure Inc.) (Copyright from Springer Nature (Publisher)) [34]

cytology were 0.833 and 0.644 [35]. These results support the clinical application of ImmunoCyt as adjuvant with urine cytology, not alone.

### 5.2.3.2 Fluorescence In Situ (FISH) Test

UroVysion (Abbott Molecular, Inc., Des Plaines, IL) is a multi-target fluorescence in situ (FISH) test for targeting common chromosomal abnormality of urothelial carcinoma. This study detects aneuploidy of chromosomes 3, 7, and 17 and loss of 9p21 loci, which express p16 tumor suppressor gene [36]. UroVysion is approved by the US FDA for initial diagnosis of bladder cancer in case of hematuria and surveillance of recurrence.

Sensitivity and specificity of FISH assay vary by studies ranged as 69–87% and 89–96% [37–39]. Recent meta-analysis shows diagnostic performance of UroVysion was higher than urine cytology [39]. UroVysion shows high diagnostic accuracy for detecting high-grade tumor and carcinoma in situ [40], and some reports support clinical usability in patients with intravesical therapy including BCG [41, 42].

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# Modifiable Risk Factor to Prevention

# 6

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## 6.1 Smoking Cessation

Smoking is a well-known risk factor for urothelial cell carcinoma. Two meta-analyses have identified the effect of active smoking and risk of bladder cancer. Van Osch et al. [1] successfully show dose-response relationship with smoking history and risk of bladder cancer by meta-analysis of 89 studies. Bladder cancer incidence was increased with smoking intensity, but there was a plateau in heavy smoker with over 15 cigarettes per day. Similar relationship was founded with pack-year and bladder cancer incidence. Bladder cancer incidence was three times higher in active smoker (RR 3.14; 95% CI 2.53–3.75) and two times higher in formal smoker (RR 1.83; 95% CI 1.52–2.14) [1]. Another meta-analysis of 90 studies has also shown similar result, with 3.37 (95% CI 3.01–3.78) and 1.98 (95% CI 1.76–2.22) pooled relative risk in active smoker and formal smoker for bladder cancer incidence [2]. Smoking cessation is the most powerful prevention method for bladder cancer, but there is still a remaining 50% chance of bladder cancer incidence in over 20-year ex-smokers [1].

Both the EAU and NICE guidelines recommend smoking cessation counseling based on studies suggesting active smoking increases risk of tumor recurrence and progression and impairs response to immunotherapy.

## 6.2 Avoid Occupational Carcinogen Exposure

Occupational exposure to chemical material is highly associated with the occurrence of bladder cancer. Cumberbatch et al. [3] analyzed multi-classes of meta-analyses for occupational carcinogen exposure using 217 studies. Standardized incidence ratio (SIR) of bladder cancer incidence was increased in 42 classes of occupation (67%) and decreased in 6 classes of occupation (10%) compared to the general population. Occupations

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that have a higher chance of exposure to aromatic amine and polycyclic aromatic hydrocarbons (PAHs) show risk ratio (RR). Risk ratio (RR) was highest in tobacco workers and dye workers with 1.72 (95% CI 1.37–2.15) and 1.58 (95% CI, 1.32–1.90). Farmers and gardeners show the lowest RR with 0.69 (95% CI 0.68–0.71) and 0.78 (95% CI 0.75–0.81). Disease-specific mortality (DSM) of bladder cancer was increased in 17 of 40 (43%) and decreased in 2 of 40 (5%) occupational classes [3]. Occupational exposure of heavy metal shows the highest risk ratio of bladder cancer mortality (10.20, 95% CI 6.89–15.09).

Avoidance or restriction of carcinogen is effective in reduction of bladder cancer. Well-known carcinogen, 4-aminodiphenyl (4-ADP), is a metabolite of nigrosine which is commonly used for printing or hair dye before the 1970s. After the restriction of 4-ADP, bladder cancer risk has fallen from 3.2–9.15-fold higher to 1.23–1.32-fold higher than the general population [3].

## 6.3 Other Modifiable Factors

Consumption of fruit (summary relative risk (SRR) 0.81; 95% CI 0.73–0.89), vegetable (SRR 0.84; 95% CI 0.72–0.96), or both (relative risk (RR) 0.83; 95% CI 0.69–1.01) shows significant reduction in incidence of bladder cancer [4]. Dose-response analysis also shows a decrement of bladder cancer incidence by 9% (RR 0.91; 95% CI: 0.83–0.99) and 8% (RR 0.92; 95% CI: 0.87–0.97) for every 200 g/day intake of fruit and vegetable [4].

One meta-analysis shows black tea intake has a protective effect on bladder cancer incidence (RR 0.79; 95% CI 0.59–0.99) [5] but no association in another meta-analysis [6]. Green tea or overall tea consumption and fluid intake show no association with bladder cancer incidence in both meta-analyses. For this reason, the relationship between tea intake and bladder cancer incidence is still a controversy.

Other dietary factors such as coffee, alcohol, milk, fish, and red meat and vitamin E do not show significant beneficial effect on bladder cancer incidence [7].

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# 7

# Transurethral Resection of Bladder Tumor

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## 7.1 Instrument

Resectoscope which is comprised by electrocautery working elements, rod-lens cystoscope, and obturator is the key instrument of TURBT. Resectoscope is larger in diameter than diagnostic cystoscope, because the working element should be passage. Resectoscope sheath with a diameter range of 20–28 Fr (French) is commonly used. Obturator is used for atraumatic passage of the resectoscope sheath through the urethra. Blind type (straight, hinged) obturator are commonly used but visual obturator can use in patients with severe BPH, who has difficult in passage of the urethra by elevation of the bladder neck. The working element is available in three types: Iglesias, McCarthy, and Baumrucker [1]. Iglesias and Baumrucker resectoscopes use spring mechanism for working element spontaneously retracted to sheath, and it allows one-hand manipulation. McCarthy resectoscope uses rack and pinion mechanism and it requires two-hand procedure.

Electrocautery electrodes with straight, angled, and loop shape for resection and ball and bar shape for coagulation are commonly used.

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Electrovaporization and laser ablation are also used in specific situation. En bloc resection of bladder tumor uses laser energy (commonly used in holmium:YAG or thulium:YAG laser) or J-shaped electrode for obtaining proper resection of bladder tumor with adjuvant tissues.

## 7.2 Procedure

### 7.2.1 Preparation

TURBT can be performed in the operation room or outpatient clinic base. In a patient in dorsal lithotomy position, both general and spinal anesthesia are acceptable. But under spinal anesthesia, obturator nerve reflex can cause bladder perforation during operation procedure, so obturator nerve block should be beneficial. Bimanual examination under general anesthesia before and after TURBT procedure provides useful information for clinical staging. Remaining palpable mass after tumor resection is suspicious for advanced disease.

### 7.2.2 Tumor Resection

Optimal infusion of bladder irrigation fluid is enough to provide clear vision of operating field. Absorption of irrigation fluid sometimes causes hyponatremia; thus using isotonic fluid is safer. Resection procedure under partially filled bladder is safer to prevent bladder perforation, because the bladder wall becomes thinner when fully filled. The anterior wall or dome masses are sometimes difficult to access. External suprapubic compression with partially filled bladder during TURBT procedure is useful.

## 7.3 Complication

Bladder perforation is a common complication of TURBT. Most of the cases occurred due to weakened bladder wall by resection site or overdistension during procedure. Incidence of perforation varies by studies but <5% [2, 3]. The bladder is not distended by excessive infusion of irrigation fluid, return fluid is inappropriately decreased, and tachycardia or abdominal distension is a suspicious sign for bladder perforation. Most of bladder perforation occurred extraperitoneally but sometimes in intraperitoneally [4]. Extraperitoneal perforation and small intraperitoneal perforation can be managed by conservative care, with catheter drainage and antibiotics [4, 5].

Hematuria is also a common complication of TURBT, incidence ranging about 3–13% [2, 3]. Tumor with large size has higher chance of hematuria. Coagulation after surgery is most important to prevent uncontrolled hematuria, and placing large caliber catheter for irrigation is also useful [1].

TUR syndrome is uncommon, but severe medical complication of TURBT is caused by massive absorption of hypotonic solution during TUR procedure. Operating time and tonicity of irrigation fluid are important for prevention of TUR syndrome; thus bipolar TURBT should be superior to monopolar TURBT. However, recent long-term follow-up result shows there was no difference of TUR syndrome incidence between monopolar and bipolar TURBT, especially in NMIBCA [6]. This result may be caused by NMIBCA that requires short resection time, advanced TUR instrument, and physician precaution for TUR syndrome.

The incidence of UTI after TURBT is variably 5–24% [3, 7, 8]. The most common pathogen is *E.coli*, but in a recent study conducted in Spain, *Pseudomonas aeruginosa* is the most frequently detected [7]. Multivariate logistic regression analysis of hospital-acquired UTI after lower urinary tract procedure shows that higher ASA score (OR 2.82; 95% CI 1.8–4.5), immunosuppression (OR 2.89; 95% CI 1.2–7.2), indwelling urinary catheter before admission (OR 2.6; 95% CI 1.6–4.2), and postoperative catheterization longer than 2 days (OR 1.74; 95% CI 1.7–4.3) were independent risk factors.

Scarring or obstruction of ureteral orifice is also reported after TURBT. Most of cases occurred by coagulation of nearby ureter orifice bladder tumor after resection. Pure cutting seldomly makes obstruction, so there should be more caution in coagulation besides ureteral orifice to avoid this complication.

## 7.4 Monopolar/Bipolar TURBT

Bipolar TURBT (B-TURBT) use hypotonic saline thus it expected superior to monopolar TURBT (M-TURBT) for prevention of TUR syndrome. TUR syndrome is related with operation time; thus tumor size and number are highly related with incidence. In MIBCA, most of the cases need short operating time; thus M-TURBT or B-TURBT show no significant difference of TUR syndrome [6, 9]. Randomized controlled trial conducted by Venkatramani et al. [10] shows two cases of TUR syndromes in M-TURBT arm, in case with 5 cm tumor size and which takes over 1 h to resection, but there were no significant differences.

Avallone et al. [6] reported 10-year follow-up data for complications of B-TURBT compared with M-TURBT. In multivariate analysis, B-TURBT shows lower overall complications than M-TURBT overall complications (0.64, 95% CI 0.44–0.9). The risk of hematuria, urinary tract infection, and urinary retention was not different with energy type. Chances of obturator reflex, bladder perforation, and hemostasis were not significantly different between B-TURBT and M-TURBT [10]. B-TURBT shows less cautery artifact of pathologic specimen was proven by RCT [10].

## 7.5 Repeated TURBT

Complete resection of bladder tumor by TURBT is important for better oncologic outcome and accurate staging. However, up to 50% of high-grade urothelial carcinoma of the bladder is under-staged in initial TURBT than radical cystectomy specimen [11–16]. Obtaining muscle layer (muscularis propria, MP) in TURBT specimen is essential for appropriate diagnosis. If there are no MP in TURBT specimen, misdiagnosis of staging rate is higher as 60–80% [13, 14]. There was no risk of under-staging in low-grade tumor of initial TURBT specimen [17]. Optimal timing for repeated TURBT is not determined, but not over 6 weeks after initial TURBT.

Residual tumor is another evidence for needs of repeated TURBT. The rate of residual tumor after initial TURBT varies from 18% to 75% [14, 18] and may depend on operator factor. Repeated TURBT is also performed in a therapeutic manner, removal of residual tumor.

Repeated TURBT shows beneficial effect before BCG treatment [19, 20]. Sfakianos et al. reported repeated TURBT before BCG therapy shows decrease in 3-month recurrence rate from 44.3% to 9.6% [20]. In this study single TURBT group shows higher recurrence rate at 5 years (OR 2.1, 95% CI 1.3–3.3) and shorter time to recurrence than repeated TURBT group [20].

T1 tumor but there are no muscularis propria (MP) specimen in initial TURBT should be considered repeated TURBT, for propriate diagnosis for muscle invasiveness (chance of T2 up staging). If T1 high-grade tumor with MP specimen, there is still a chance of upstaging to MIBC, and restaging TURBT is recommended. Concomitant CIS is also considered for repeated TURBT for manner of removal of residual tumor. There are still controversies but Ta high grade or multiple, large (over 3 cm) also have benefit of repeated TURBT.

## 7.6 Transurethral Prostate Biopsy

The incidence of prostatic urethral involvement of urothelial carcinoma ranged 15–57% in cystectomy patients [21–24]. Shen et al. [21] reported 32% of the 214 radical cystoprostatectomy specimens show prostatic involvement, and 43% of them were carcinoma in situ (CIS). Nixon et al. [22] demonstrated 30 of the 192 patients (15.6%) who underwent radical prostatectomy have prostatic involvement. Multiple variable logistic regression model shows the odds of prostatic urethral involvement was 12- and 15-fold higher in the presence of multifocal bladder tumor and CIS.

Beside the usefulness of transurethral prostate biopsy, routine exam is not indicated. If there are CIS lesion, multifocal bladder tumor, and visible abnormalities of the prostatic urothelium, prostatic urethral biopsy should be performed for proper diagnosis and treatment.

Prostatic urethral biopsy also shows beneficial effect for BCG penetration [25]. Prostatic CIS lesion can be treated by BCG instillation alone [26]. However, transurethral resection of the prostate provokes transitional bladder neck incompetency and provides longer contact time of BCG to prostatic CIS lesion [27]. It makes response rates to BCG increase. Stromal invasion of the prostate is a poor prognostic factor and radical cystoprostatectomy is the treatment of choice.

Obtaining prostatic urethral sample of 5 and 7 o'clock position above verumontanum, by using electrocautery loop dissection (Fig. 7.1). This location involved prostatic ducts which show higher risk for CIS involvement [28]. Rundstedt et al. [29] also described negative in preoperative prostatic urethral biopsy patient shows higher negative rate for intraoperative frozen biopsy. For detecting apical involvement condition, TUR prostate biopsy shows to be more sensitive than intraoperative frozen section by 83.3% and 66.7% [29]. This is preliminary report, but if there are negative in TUR prostate biopsy, operator does not need intraoperative frozen biopsy to avoid false-positive result and save operating time.

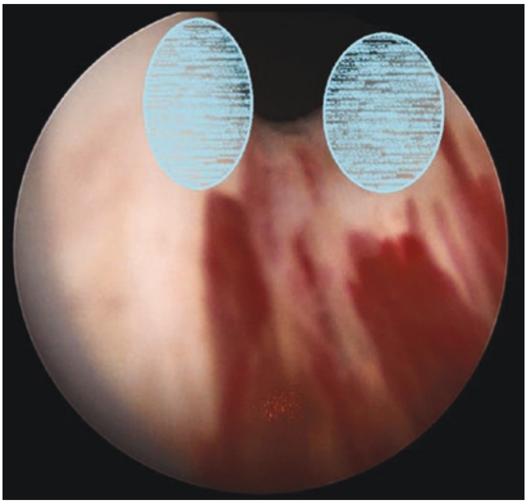

**Fig. 7.1** Transurethral biopsy of prostate is considered in suspicious CIS lesion, but there were no visible lesions in cystoscopy. Obtaining 5 and 7 o'clock position of the bladder neck to verumontanum by electrocautery loop

## 7.7 Bladder Random Biopsy (Mapping Biopsy)

Carcinoma in situ is flat, high-grade urothelial carcinoma with concomitantly high chance of papillary urothelial carcinoma. However, CIS is not easily detected by conventional cystoscopy, so this is why urologist performs random biopsy during TURBT. Positive rate of bladder random biopsy is not excellent, ranging 8–23% [30, 31]. For this reason, routine exam of bladder random biopsy is still in controversy. Two major EORTC studies collect evidence of effectiveness of routine random biopsy [32, 33]. Meijden et al. found only 10% of patients show positive result of bladder random biopsy in Ta and T1 urothelial carcinoma of the bladder and concluded that random biopsies do not contribute to the staging or treatment selection in Ta and T1 patients. May et al. [33] found similar incidence of positive rate as 12% of patients underwent random biopsy of Ta, T1, and Tis bladder cancer. However, conclusion was somewhat different in the previous study. In 14 patients, initial TURBT fails to find malignancy, but random biopsy is successful to find urothelial carcinoma. Clinical upstaging after random biopsy was found to be 4%, 15%, and 5% for Ta, T1, and Tis urothelial carcinoma. Overall 6.8% of patients change therapy due to random biopsy; thus authors recommended routine biopsy during TURBT [33].

NCCN recommend random biopsy in the case of high-grade, sessile, or CIS-like lesion presenting bladder cancer. EAU also suggest suspicious CIS lesion, with negative findings in cystoscopy but positive in cytology. Random biopsy should include trigone, dome, left, right, anterior, and

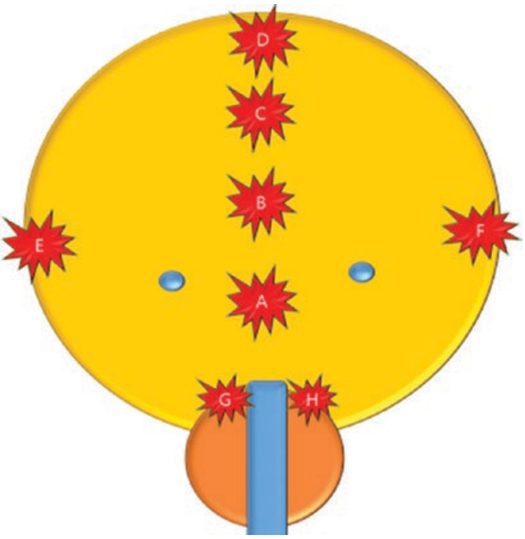

**Fig. 7.2** Map for bladder random biopsy. Random biopsy should be performed in trigone (A), posterior (B), dome (C), anterior (D), and both lateral sides of the bladder wall (E and F). Most importantly prostate biopsy (G and H) should be performed with transurethral resection, not by cold cup biopsy

posterior bladder wall specimen (Fig. 7.2). Obtaining prostatic urethral specimen by TUR resection is better than cold cup biopsy.

## 7.8 Routine Biopsy after BCG

Intravesical bacillus Calmette-Guérin (BCG) instillation therapy provides better oncological outcome in high-grade T1 disease. Standard BCG induction therapy takes 6 times instillation weekly after complete TUR resection of bladder tumor. Assessing treatment response after BCG therapy is sometimes difficult because of benign changes related to BCG. Swietek et al. reported that in 180 patients who underwent random biopsy after BCG therapy, 32% of bladder biopsy was positive and 30% of visible tumor found. Erythematous lesion was 20%, and positive predictive value (PPV) of erythema was 15% with negative cytology and 56% with positive cytology. The PPV in normal in cystoscopy with negative cytology and erythematous lesion with negative cytology was just 5% and 9%; thus in this situation, routine biopsy is not recommended.

## 7.9 En Bloc Resection of Bladder Tumor

The current gold standard therapy is still TURBT by electrocautery loop; en bloc resection of bladder tumor (ERBT) is an advanced technique to obtain three goals: to improve resection quality, lower perioperative complication rates, and decrease recurrence rates at resection sites. ERBT commonly use laser device (holmium:YAG and thulium:YAG) for dissection, but Japan researchers developed J-shaped needle of electrocautery instrument [34]. ERBT focused on obtaining clear pathologic specimen of muscle layer for accurate diagnosis; muscle layer should be dissected minimally using energy device for lowering cautery artifact.

Multicenter study of Europe shows 97% of ERBT specimen contained muscle layer [35]. In a recent meta-analysis, ERBT and conventional TURBT do not show difference in operation time [36]. ERBT provide shorter hospitalization time and catheterization time than TURBT group. Complications were also lower in ERBT at a risk of bladder perforation ($P = 0.004$), bladder irritation ($P < 0.01$), and obturator nerve reflex ($P < 0.01$). Oncological outcome is also superior in ERBT group for 24-month recurrence rate (OR 0.66, 95% CI 0.47–0.92). In intravesical mitomycin instillation group, 24-month recurrence rate was also lower in ERBT group.

Laser device is more optimal to perform ERBT, but in hospital without laser device, electronic ERBT by J-shaped needle can be alternative. A comparison between laser ERBT and electronic ERBT shows there was no difference between obtaining muscle layer and oncological outcome of recurrence. However, switch to conventional TURBT was significantly higher in electronic ERBT group than laser-ERBT group (26.3 vs. 1.5%) [35].

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# 8

# Intravesical Instillation Therapy

Jungyo Suh

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## 8.1 Immediate Post-TURBT Intravesical Chemotherapy

### 8.1.1 Efficacy

Sylvester et al. [1] conducted a meta-analysis of seven randomized controlled trials (RCTs) to determine the clinical effects of immediate post-TURBT [post–transurethral resection of a bladder tumor] intravesical chemotherapy (PIC) in Ta-T1-grade tumors. The odds of recurrence were decreased by 39% with PIC versus TURBT alone (odds ratio (OR) 0.61, $p < 0.0001$). Both single- and multiple-tumor cases showed beneficial effects of PIC compared with TURBT alone, but 65% of patients in the multiple-tumor group experienced a recurrence. Immediate PIC prolonged the recurrence-free interval by 38%, and the early recurrence rate was reduced by 12% in the non-muscle-invasive bladder cancer (NMIBC) group [2]. In a recent updated analysis of pTa-T1 bladder cancer, conducted by Sylvester et al [3], a PIC dose was not effective in the group with a high risk of recurrence, especially in those

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with a European Organization for Research and Treatment of Cancer (EORTC) recurrence score greater than 5 or a recurrence rate of more than once per year.

### 8.1.2 Protocol

Immediate PIC instillation may be done to reduce reimplantation of floating tumor cells into the normal epithelium. Floating tumor cells have been shown to reimplant within a few hours after TURBT and become covered with extracellular matrix [4]. For this reason, immediate PIC should proceed within (at most) 24 h after TURBT.

Mitomycin C (MMC), epirubicin, and valrubicin are commonly used, and gemcitabine is considered a new agent for PIC. MMC is the most commonly used PIC agent and is considered the first-line therapy [5]. MMC, epirubicin, and pirarubicin have all shown beneficial effects in prolonging the time to recurrence, but there have been no randomized comparisons of these drugs. The optimal dosage and protocol have also not yet been clarified; the European Association of Urology (EAU) guideline suggests MMC 20–40 mg as a standard dose.

A meta-analysis by Sylvester et al. [1] noted that a single instillation may not be enough for patients with multiple NMIBC tumors. This subgroup also benefited from PIC (OR 0.44), but their recurrence rate was still as high as 65.2%.

## 8.2 Induction and Maintenance Intravesical Chemotherapy

### 8.2.1 Chemotherapeutic Agents

Many chemotherapeutic agents are used for induction and maintenance intravesical therapy. Thiotepa is a nonspecific alkylating agent and was the first drug approved by the US Food and Drug Administration (FDA) as intravesical therapy for NMIBC. Thiotepa is chemically similar to nitrogen mustard; it is absorbed through the bladder mucosa and causes myelosuppression. Its side effects are dose dependent. In a recent meta-analysis, patients who received thiotepa had a lower risk of bladder cancer recurrence than those who received only TURBT, but the difference was not significant, and the risks of progression and mortality also showed no differences [6].

MMC is another alkylating agent but is rarely absorbed by the bladder mucosa and thus shows a lower risk of systemic side effects than thiotepa. MMC is the most widely used intravesical chemotherapeutic agent. MMC instillation has been reported to decrease the risk of recurrence (risk ratio (RR) 0.68, 95% confidence interval (CI) 0.55–0.83) in comparison with TURBT alone. Both single instillation (RR 0.45, 95% CI 0.22–0.91) and maintenance therapy (RR 0.71, 95% CI 0.60–0.84) are effective. The effect on bladder cancer progression is significant [6].

Doxorubicin is an anthracycline drug, with a high molecular weight. It is also rarely absorbed by the bladder mucosa; thus systemic side effects are not common. Intravesical instillation of doxorubicin has been shown to reduce the risk of recurrence but does not significantly reduce the risks of progression and mortality.

Epirubicin is another type of anthracycline drug; it is more effective and has fewer side effects than doxorubicin. Patients receiving epirubicin in addition to TURBT reportedly have a reduced risk of recurrence in comparison with TURBT alone (RR 0.63, 95% CI 0.53–0.75). The relative risks of cancer progression, cancer-specific mortality, and all-cause mortality with TURBT plus epirubicin versus TURBT alone are not clear [6].

Gemcitabine is a nucleoside analog and a commonly used chemotherapy agent for advanced bladder cancer. Current evidence suggests that a single dose of gemcitabine is not as effective as multiple doses [7]. The recurrence and progression rates have been reported to be lower with gemcitabine than with MMC, but the difference was not significant [7]. Gemcitabine is as effective as instillation of bacillus Calmette–Guérin (BCG) in intermediate-risk patients but is inferior to BCG in high-risk patients [7].

### 8.2.2 Protocol

The optimal dosage and schedule of intravesical instillation are still controversial. The EAU guideline recommends intravesical chemotherapy in intermediate-risk patients, with maintenance therapy for 1 year [8]. There is no consensus on the duration and intensity of intravesical chemotherapy; however, maintenance therapy for longer than 1 year is not recommended. The American Urological Association (AUA) guideline recommends induction of intravesical therapy in patients with multifocal, large-volume Ta or recurrent Ta low-grade tumors, but states that maintenance therapy is optional. Only the EAU guideline documents optimization methods for intravesical MMC therapy (dehydration, urinary alkalinization, and use of higher concentrations).

The dosage of MMC varies from 20 to 60 mg, but the most common dosage is 40 mg with 40 mL of saline. The most usually acceptable protocol is 8-week administration followed by monthly instillation for 1 year. The dosage of doxorubicin ranges from 10 to 100 mg, and a protocol of 20–50 mg for 8 weeks of induction therapy with or without subsequent 1-year maintenance therapy is associated with a significant reduction in recurrence. Epirubicin 50 mg given for 8 weeks followed by monthly instillation for 1 year has shown efficacy equal to that of an immediate single instillation in reducing bladder cancer recurrence.

### 8.2.3 Optimization

MMC is the most commonly used intravesical chemotherapeutic agent, but the optimal approach to obtain higher therapeutic efficacy has not yet been clearly established. The current pharmacological protocol is based on the findings of one RCT [9], with an increased drug concentration, increased drug contact time, and urinary alkalization.

Electromotive drug administration (EMDA) and chemohyperthermia (C-HT) therapy are novel methods for enhancing delivery of MMC to penetrate the protective layer of the bladder urothelium. EMDA uses an electrical field to enhance drug delivery. The first RCT was conducted by Di Stasi et al. in 2003 [10] and compared the effectiveness of EMDA-MMC, passive diffusion (PD) of MMC (PD-MMC), and BCG in high-risk NMIBC. EMDA-MMC showed better results than PD-MMC, equivalent to those of BCG therapy. The most recent RCT compared EMDA-MMC before TURBT, PD-MMC after TURBT, and TURBT alone, and showed better oncological outcomes with EMDA-MMC [11], which was associated with a lower recurrence rate (38%) than PD-MMC (59%) or TURBT alone (64%). Moreover, the disease-free interval was longer with EMDA-MMC (52 months) than with PD-MMC (16 months) or TURBT alone (12 months).

C-HT using localized heating of bladder tissue increases the permeability of the cell membrane and blood perfusion of the tissue. C-HT is also expected to directly damage floating bladder tumor cells through DNA damage, causing cell apoptosis. The heating is generated by a probe inserted into the bladder with a microwave energy radiofrequency of around 915 MHz [5]. The most recent systematic review [12] showed a 59% risk reduction with MMC C-HT versus MMC alone.

## 8.3 Intravesical BCG Immunotherapy

### 8.3.1 Introduction

BCG instillation therapy, which uses a live attenuated *Mycobacterium bovis* strain, is the most effective adjuvant treatment after TURBT in intermediate- to high-risk NMIBC patients. Several meta-analyses have shown favorable oncological outcomes of adjuvant intravesical BCG instillation compared with TURBT alone [6, 13, 14]. In comparison with intravesical chemotherapy, BCG therapy was superior to doxorubicin, epirubicin, and thiotepa in lowering the recurrence rate [6]. The risks of progression and mortality could not be assessed. MMC is the only intravesical therapy that has shown a similar effect in reducing the recurrent rate. The risks of progression, all-cause mortality, and bladder cancer-specific mortality also showed no difference.

### 8.3.2 BCG Strain

One meta-analysis compared the therapeutic efficacy of five different BCG strains [14]: Tice (Organon Inc., West Orange, NJ, USA); Connaught (Connaught Laboratories, Toronto, ON, Canada); Pasteur (Aventis Pasteur, Brussels, Belgium); RIVM (National Institute for Public Health and the Environment, Bilthoven, the Netherlands); and A. Frappier (Institut Armand-Frappier, Laval, QC, Canada). The Tice strain was most frequently used (in 38.9% of patients). There was no significant difference in efficacy between BCG strains.

A more recent prospective RCT comparing the Tice and Connaught strains came to a different conclusion. The Connaught strain was significantly more effective for recurrence-free survival [15]. To clarify the effect of the BCG strain on treatment, further study is needed.

### 8.3.3 Protocol

Induction of a BCG instillation was first introduced by Morales in 1976, consisting of six weekly doses of 120 mg each [16]. Induction therapy is associated with reductions in recurrence, progression, and mortality within 10 years, but its effect is not significant at 15 years. For optimal efficacy, maintenance BCG therapy should be given. Regardless of the induction therapy, many different maintenance schedules are used [17].

The optimal protocol of maintenance BCG therapy has not yet been confirmed. The only clear conclusion is that a BCG maintenance schedule needs to be continued for at least 1 year to be superior to MMC therapy [18]. Several studies have shown that 3-weekly BCG maintenance instillations after 6-week induction therapy reduce the risks of recurrence and progression of bladder cancer [17–21]. Another maintenance regimen designed by the Southwest Oncology Group (SWOG) consists of three once-weekly intravesical instillations of BCG at 3, 6, 12, 18, 24, 30, and 36 months after a 6-week induction phase [17].

The EORTC Genito-urinary Cancers Group (EORTC-GU) compared the efficacy and toxicity of full-dose therapy and reduced-dose therapy (using a one-third dose) over 1-year and 3-year periods [21]. There was no significant dose-related difference in toxicity; thus, 1 year of full-dose maintenance therapy should be beneficial for intermediate-risk patients. For treatment of high-risk patients, 3 years of full-dose BCG therapy was superior to 1 year of full-dose therapy in reducing the risk of recurrence. However, there were no long-term differences in disease progression and survival between the two groups.

### 8.3.4 Adverse Effects

Intravesical BCG treatment carries more risk of complications than intravesical chemotherapy [14]. Most of the complications are local side effects, which are easily treated. Fewer than 5% of patients experience severe systemic adverse events with a need to stop the instillation, and most of them are treated effectively [22]. Most of the systemic side effects occur within the first 6 months of treatment; after that the incidence decreases [22]. Maintenance treatment is not associated with an increase in adverse events (local and systemic) [22]. For this reason, fear of increasing toxicity risks should not discourage use of maintenance BCG therapy.

Asymptomatic bacteriuria, leukocyturia, and microscopic hematuria are not contraindications to BCG therapy [23]. About 25% of patients show significant bacteriuria during BCG instillation therapy; in one study, one patient (1.6%) developed a febrile urinary tract infection (UTI) [23]. Antibiotic prophylaxis for asymptomatic bacteriuria is not necessary during BCG instillation [24].

Because BCG treatment uses an attenuated but live *Mycobacterium bovis* strain, caution is needed when it is used in immunocompromised patients. According to the EAU guideline, BCG treatment is absolute contraindicated (1) during the first 2 weeks after TURB; (2) in patients with visible hematuria; (3) after traumatic catheterization; and (4) in patients with a symptomatic UTI.

### 8.3.5 BCG-Unresponsive NMIBC

BCG-unresponsive NMIBC is defined as “persistent high-grade disease or recurrence within 6 months of receiving at least two courses of intravesical BCG (at least 5 of 6 induction doses and at least 2 of 3 maintenance doses); or T1 high-grade disease at the first evaluation following induction BCG alone (at least 5 of 6 induction doses).” This novel category is important for identifying truly defined failure of BCG therapy, which necessitates another optimal treatment to replace BCG immunotherapy. In this specific group of high-risk urothelial carcinoma patients, the only standard therapy is radical cystectomy.

“BCG-unresponsive” NMIBC (Figs. 8.1 and 8.2) is a novel subgroup of “BCG failure,” which includes “BCG intolerance,” “BCG refractory,” and “BCG relapse” [25]. The term “BCG intolerance” means patients cannot receive BCG instillation because of adverse effects of BCG. “BCG refractory” indicates the presence of persistent high-grade cancer within 6 months after induction therapy or progression of cancer within 3 months after the start of induction therapy [25]. “BCG relapse” indicates cancer recurrence after achievement of a disease-free state within 6 months after treatment.

### 8.3.6 BCG Shortages

Patients with high-risk NMIBC are a challenging group to treat, with high risks of recurrence and progression. The treatment options for high-risk NMIBC are intravesical BCG, intravesical chemotherapy, and radical cystectomy. Of these available options, intravesical BCG instillation is considered the first-line therapy for high-risk NMIBC patients. Intravesical BCG therapy shows good oncological outcomes, reducing and delaying tumor progression.

Although the clinical benefit of intravesical BCG has been shown, another problem can arise that is beyond the scope of treatment guidelines. BCG shortages are caused by supply and demand mismatching, difficulties in manufacturing BCG, and increasing demand for BCG for bladder cancer treatment. A recent worldwide BCG shortage was provoked by a halt in production of a BCG strain by a major manufacturing company. Supplies subsequently slowly recovered; however, because of supply and demand mismatching, BCG shortages are likely to occur again in the near future.

For this reason, second-line treatment options for use during BCG shortages should be suggested. Option 1 is maintenance of full-dose BCG for 1 year in patients without carcinoma in situ (CIS) lesions; this option does not lead to more tumor progression but there is a higher recurrence rate in very high-risk patients [21]. Option 2 is reduced-dose BCG induction (using a one-third dose) and maintenance for 1 year; this protocol has been approved by the EORTC and shows no difference in cancer progression in comparison with full-dose therapy. Option 3 is intravesical MMC as an alternative to intravesical BCG; intravesical MMC is not significantly inferior to BCG in preventing progression [6, 19]. Option 4 is use of novel methods to enhance MMC delivery; C-HT and EMDA are promising examples. Option 5 is use of intravesical gemcitabine, which is another promising intravesical therapeutic agent; induction of 1–2 g in 50 cc of sterile water over 90 min and a monthly maintenance protocol are recommended. Option 6 is radical cystectomy, which is another good alternative to intravesical BCG, especially in terms of the oncological outcome.

## 8.4 New Definition of Disease Progression

The definition of disease progression has changed to a more general concept. The old criteria defined disease progression of NMIBC after BCG induction therapy as progression of muscle

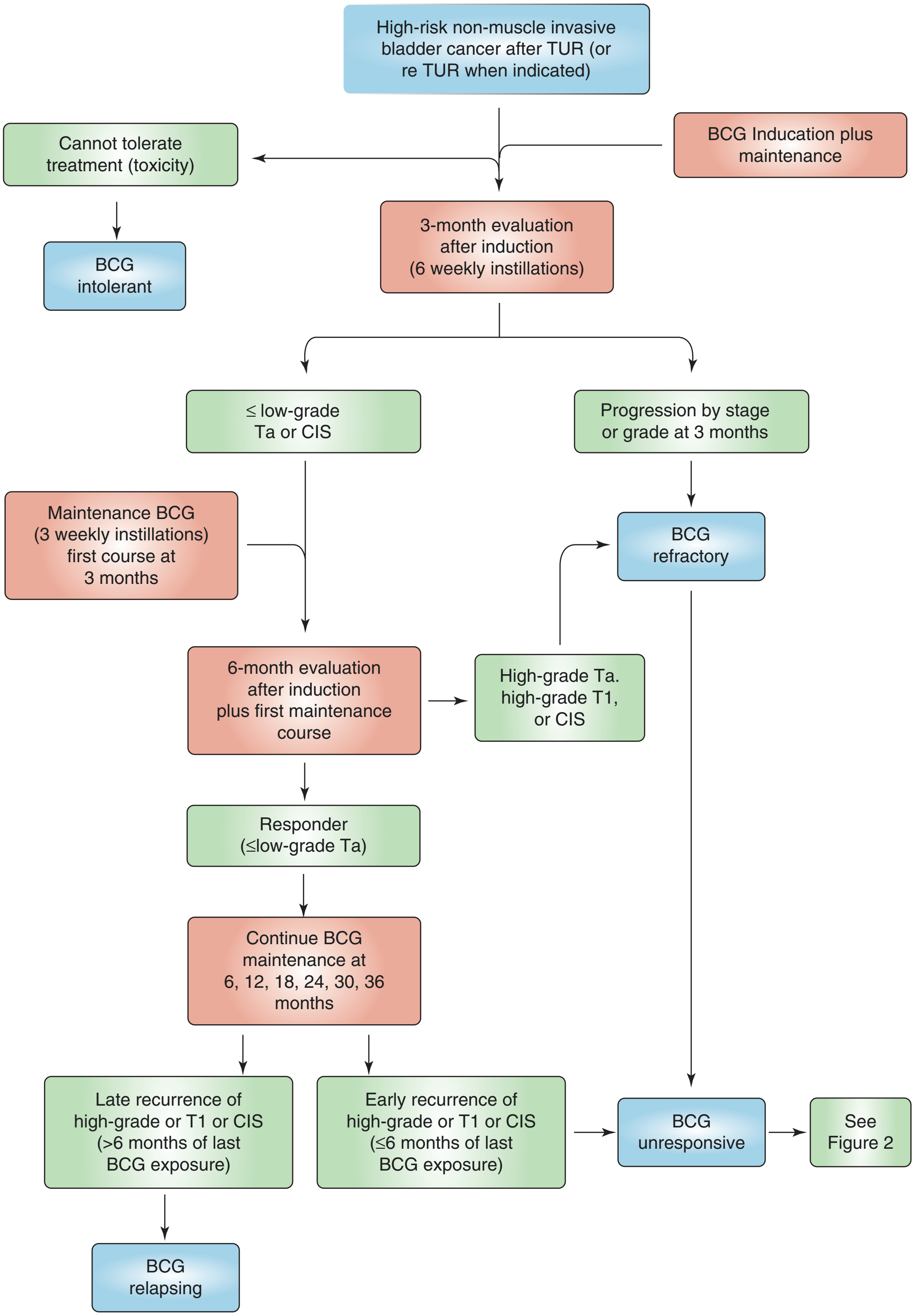
High-risk non-muscle invasive bladder cancer after TUR (or re TUR when indicated)
BCG Inducation plus maintenance
Cannot tolerate treatment (toxicity)
BCG intolerant
3-month evaluation after induction (6 weekly instillations)
≤ low-grade Ta or CIS
Progression by stage or grade at 3 months
Maintenance BCG (3 weekly instillations) first course at 3 months
BCG refractory
6-month evaluation after induction plus first maintenance course
High-grade Ta. high-grade T1, or CIS
Responder (≤low-grade Ta)
Continue BCG maintenance at 6, 12, 18, 24, 30, 36 months
Late recurrence of high-grade or T1 or CIS (>6 months of last BCG exposure)
Early recurrence of high-grade or T1 or CIS (≤6 months of last BCG exposure)
BCG unresponsive
See Figure 2
BCG relapsing

**Fig. 8.1** Classification of patients with high-risk non-muscle-invasive bladder cancer (*NMIBC*) after intravesical bacillus Calmette–Guérin (*BCG*), and types of BCG failure. Distinct categories of clinical responses to BCG are determined by the treatment duration/sequence, the clinical response, and the timing of the clinical response, which are represented in the flowchart. *CIS* carcinoma in situ, *TUR* transurethral resection. (Copyright Springer-Nature [25])

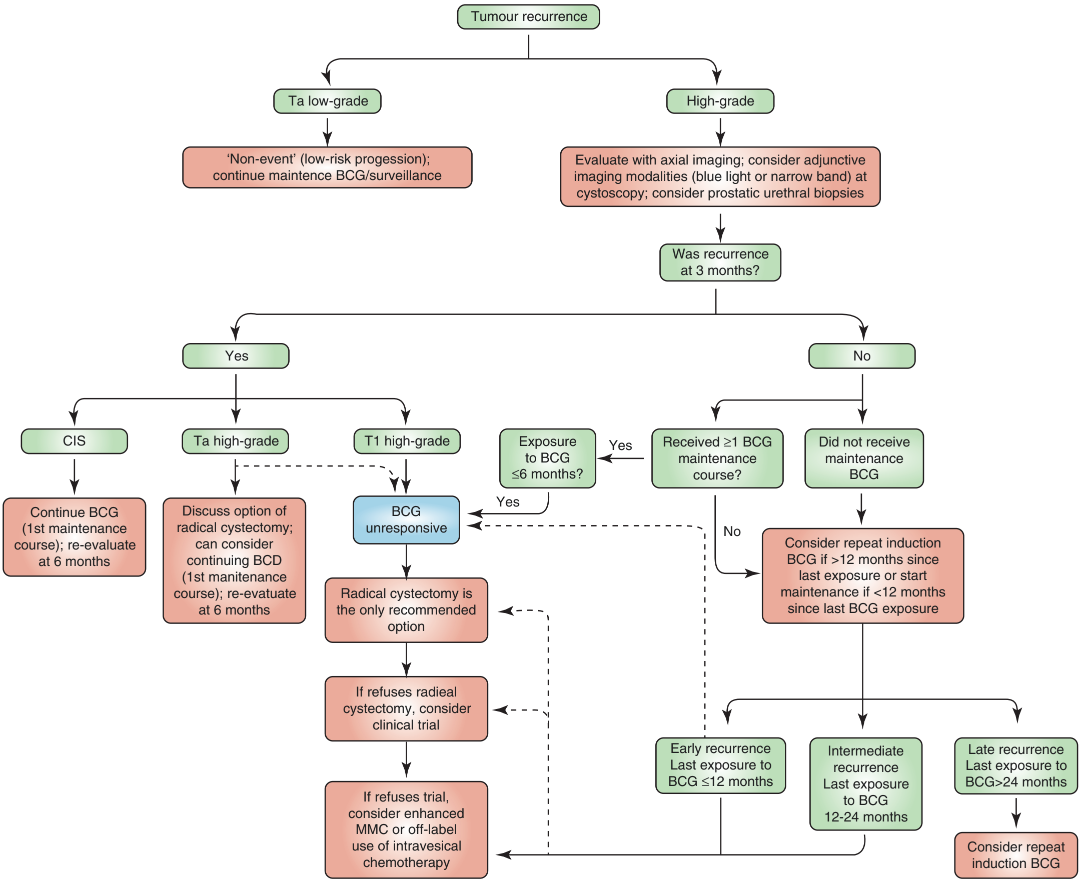
Tumour recurrence
Ta low-grade
High-grade
'Non-event' (low-risk progession); continue maintence BCG/surveillance
Evaluate with axial imaging; consider adjunctive imaging modalities (blue light or narrow band) at cystoscopy; consider prostatic urethral biopsies
Was recurrence at 3 months?
Yes
No
CIS
Ta high-grade
T1 high-grade
Exposure to BCG ≤6 months?
Yes
Received ≥1 BCG maintenance course?
Did not receive maintenance BCG
Continue BCG (1st maintenance course); re-evaluate at 6 months
Discuss option of radical cystectomy; can consider continuing BCD (1st manitenance course); re-evatuate at 6 months
Yes
BCG unresponsive
No
Consider repeat induction BCG if >12 months since last exposure or start maintenance if <12 months since last BCG exposure
Radical cystectomy is the only recommended option
If refuses radieal cystectomy, consider clinical trial
If refuses trial, consider enhanced MMC or off-label use of intravesical chemotherapy
Early recurrence Last exposure to BCG ≤12 months
Intermediate recurrence Last exposure to BCG 12-24 months
Late recurrence Last exposure to BCG>24 months
Consider repeat induction BCG

**Fig. 8.2** Management approaches for patients with non-muscle-invasive bladder cancer (*NMIBC*) who do not respond to bacillus Calmette–Guérin (*BCG*) or who experience recurrence after BCG are determined by the timing and duration of prior BCG therapy, as well as the timing of clinical recurrence. *CIS* carcinoma in situ, *MMC* mitomycin C. (Copyright Springer-Nature [25])

invasiveness or metastasis only. The new criteria for progression include all of the following definitions: an increased T stage, prostate involvement, progression to high-grade disease, and the old criteria of invasion to the muscle layer or metastasis. The new criteria for progression of BCG are listed below:

1. Increase in the T stage from CIS or Ta to high-grade T1 (lamina propria (LP) invasion)
2. Development of T2 or greater, lymph node (N+) disease, or distant metastasis (M1)
3. T1 (LP invasion) or T4 (stroma invasion) of the prostate
4. Increase in the grade from low to high grade

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# Early Radical Cystectomy

# 9

Jungyo Suh

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## 9.1 Indications for Early Radical Cystectomy

The American Urological Association (AUA) guidelines recommend early radical cystectomy in patients with non-muscle invasive bladder cancer (NMIBC) with variant histology, which is considered a poor prognostic factor. Early cystectomy is also recommended for patients with T1 tumors with lymphovascular invasion (LVI), those with carcinoma in situ (CIS), and those with persistent T1 high-grade disease after repeated resections. It is also recommended that cystectomy be performed in high-risk patients with bacillus Calmette-Guérin (BCG) failure within 1 year of treatment—specifically those with persistent or recurrent disease after two induction cycles of BCG or BCG induction and maintenance [1].

The European Association of Urology (EAU) guidelines also recommend early cystectomy in patients with a high risk of progression, i.e., T1 high-grade tumor with CIS and multifocal, large (over 3 cm), or recurrent tumors. Early cystectomy is also recommended for patients with LVI and variant histology. The EAU guidelines recommend that T1 high-grade tumor with prostatic CIS urethral involvement also be considered for radical cystectomy (Table 9.1).

### 9.1.1 Very High-Risk Patients

#### 9.1.1.1 Lymphovascular Invasion

In microscopic pathologic specimens obtained from transurethral resection of bladder tumor (TURBT), the presence of tumor cells in the lymphatic and vessel walls is called LVI. In many other malignancies, the presence of LVI is considered a poor prognostic marker of advanced disease. In urothelial carcinoma of the bladder, the negative predictive role of LVI in NMIBC is well established in radical cystectomy patients

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**Table 9.1** EAU and AUA guidelines for early cystectomy in non-muscle invasive bladder cancer

| Guideline | Indications | Evidence strength |
|---|---|---|
| AUA | T1 high-risk patients<br>T1 tumor with LVI, CIS, or variant histology (poor prognostic factor) | Low |
| | High-risk patients with persistent/recurrent disease within 1 year following two induction cycles of BCG or BCG maintenance | Low |
| | Ta low- or intermediate-risk disease patients should not receive cystectomy until bladder-preserving modalities have failed | Expert opinion |
| EAU | T1HG with CIS, LVI, variant histology, prostatic urethral CIS, and multiple, large tumors | LE 3 |
| | In BCG-refractory patients early cystectomy is strongly recommended | LE 3<br>*AUA* American Urological Association, *EAU* European Association of Urology, *BCG* bacillus Calmette-Guérin, *Ta*,…*CIS* carcinoma in situ, *LVI* lymphovascular invasion, *HG*…, *LE*… |

*Ta* Pathologic T a stage urothelial carcinoma. The cancer is a non-invasive papillary carcinoma (Ta). It has grown toward the hollow center of the bladder but has not grown into the connective tissue or muscle of the bladder wall, *HG* High grade, *LE* Level of Evidence

[2]. A recent meta-analysis successfully revealed the prognostic role of LVI in TURBT specimens from patients with NMIBC [3]. The presence of LVI in TURBT specimens is significantly correlated with pathologic upstaging (pooled odds ratio [OR] = 2.21; 95% confidence interval [CI], 1.44–3.39), recurrence-free survival (pooled hazard ratio [HR] = 1.47; 95% CI, 1.24–1.74), and progression-free survival (pooled HR = 2.28; 95% CI, 1.45–3.58), respectively.

Lymphovascular invasion is a significant prognostic factor in disease progression [4]. Martin-Doyle et al. [4] found, by meta-analysis of four LVI studies, that LVI was a significant prognostic factor for recurrence, progression, and cancer-specific survival, with pooled HRs of 1.68 (95% CI 1.34–2.11), 2.88 (95% CI 1.61–5.14), and 2.08 (95% CI 1.44–2.99), respectively. Another study showed that LVI was rarely found in TURBT specimens from cT1 tumors and that the presence of LVI was related to nodal metastasis in matched cystectomy specimens [5].

These lines of evidence suggest that LVI in TURBT specimens means that these populations are clinically under-staged and have a high risk of progression. For this reason, the presence of LVI in TURBT specimens from patients with high-grade urothelial cell carcinoma is considered to represent a very high risk for these patients, for whom early cystectomy needs to be considered.

#### 9.1.1.2 Concomitant Carcinoma in Situ

Carcinoma in situ (CIS) is a flat papillary, high-grade, noninvasive lesion with aggressive characteristics. The clinical presentation of CIS is both isolated and synchronous, and it can occur in any part of the urothelium [6]. The presence of CIS is related to the recurrence and progression of urothelial carcinoma. Diagnosis is the most challenging part of the management of CIS. Novel diagnostic cystoscopy shows promising results; however, most diagnoses of CIS are made from conventional cystoscopic resections of suspicious lesions or from random biopsies.

The first-line treatment of isolated CIS is intravesical BCG immunotherapy. Primary CIS with treatment failure of intravesical BCG should be considered for radical cystectomy [6]. However, there is still no consensus regarding the performance of immediate radical cystectomy for isolated CIS lesions. A combined analysis of six European Organisation for Research and Treatment of Cancer (EORTC) trials showed that concomitant CIS was the most important prognostic factor in high-grade (T1G3) urothelial carcinoma [7]. The 5-year progression rate of T1G3 tumors without CIS was 29% but this increased to 74% in patients with concomitant CIS lesions.

#### 9.1.1.3 Prostatic Urethral Involvement

Prostatic urethral involvement is another important prognostic factor in NMIBC. Isolated prostatic CIS is uncommon in NMIBC, occurring in less than 10% of cases; most prostatic CIS is related to high-grade urothelial carcinoma of the bladder [8]. Prostatic stromal CIS is considered to be T4a disease and shows a worse 5-year survival outcome (12%) than prostate urethral CIS (40%), lamina propria involvement (36%), and ductal CIS (35%) [9]. For determining the depth of prostate invasion in patients with prostate CIS, staging transurethral resection of the prostate is recommended.

#### 9.1.1.4 Unfavorable Histologic Variants

In some cases of urothelial carcinoma with unfavorable histologic variants, more aggressive treatment is needed, even in those with NMIBC [10]. Macropapillary, sarcomatoid, and plasmacytoid variants of urothelial carcinoma are uncommon but show poor prognosis.

Macropapillary urothelial carcinoma usually shows invasive features; its incidence varies by studies from 0.6 to 6% [11]. The response of the macropapillary variant to BCG is poor; only 19% of patients obtained disease-free survival at an average 30-month follow-up after BCG therapy, and the 5-year survival rate was higher in those with early cystectomy [12].

Sarcomatoid variant is also uncommon; less than 1% of urothelial carcinoma cases show this variant [10]. Sarcomatoid variant also shows a poor prognosis, presenting with a more advanced stage than urothelial carcinoma without histologic variant at diagnosis [13]. The 5-year survival rate for patients with sarcomatoid variant who underwent radical cystectomy was only 20%; in most of the reported cases the patients needed radical cystectomy with adjuvant chemotherapy [14].

Plasmacytoid variants present with undifferentiated pathologic features. The response of these patients to BCG immunotherapy is not clear; this variant shows aggressive features with a high risk of recurrence through the fascial plane [15]. In patients with the plasmacytoid variant, early cystectomy may be the only available treatment option for the management of recurrence [10].

### 9.1.2 BCG Failure Patients

Response to BCG treatment is an important prognostic factor. Intravesical BCG instillation shows good therapeutic efficacy and prognosis; however, in some patients BCG treatment shows no effects; i.e., so-called BCG failure. Up to 41.3% of patients treated with BCG developed recurrence, and 19.8% showed progression within 5years of maintenance BCG therapy [16]. In patients with this specific condition, radical cystectomy should be considered.

The EAU guidelines strongly recommend early cystectomy for BCG failure patients; other guidelines, analyzed by Tan et al. [17], suggest radical cystectomy or another induction therapy for these patients. Although the efficacy of a second induction therapy is not well determined, it is a good option for patients who do not want a radical operation. However, all guidelines analyzed by Tan et al. [17] agreed that radical cystectomy should be performed when a second induction BCG also failed.

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# Part II

# Muscle Invasive and Metastatic Bladder Cancer

# Radical Cystectomy

# 10

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## 10.1 Transurethral Resection of Bladder Tumor (TURB)

TURB alone is not sufficient for MIBC treatment. It is generally known that recurrence and progression rates of bladder cancer increase (Table 10.1). TURB in patients with MIBC can only be considered for patients who refuse or cannot perform open cystectomy or who have a bladder preserving approach. Bladder-sparing treatment was designed to improve the quality of life of MIBC patients who were not undergoing surgery.

## 10.2 Neoadjuvant Chemotherapy

The standard treatment of neoadjuvant in MIBC patients is cisplatin-based combination therapy. Neoadjuvant chemotherapy is aimed at reducing locoregional and distant recurrence and reducing microinvasion [4]. There are several arguments for the suitability of neoadjuvant chemotherapy. First, the patient is better tolerated with chemotherapy because the preoperative physical condition is better. And adjuvant chemotherapy is more likely to be delayed due to postoperative complications and weakness. Second, when the time is a little quick, the burden of disease is small. This timely and early chemotherapy may help to reduce microinvasion. Third, neoadjuvant chemotherapy has the potential of downstage. It makes a favorable pathological status and increases the likelihood of complete resection. And it reduces the likelihood of a positive surgical margin; this prevents local recurrence after radical cystectomy. Fourth, by performing chemotherapy with the tumor in vivo, clinician can assess the individual's chemosensitivity in vivo. Disadvantages of neoadjuvant chemotherapy are excessive treatment and delay of treatment. It can delay treatment in patients who do not respond to chemotherapy [5–7].

**Table 10.1** Prospective studies of TURB monotherapy for the treatment of MIBC

| Study | No. of patients | Stage | Follow-up | Outcomes |
|---|---|---|---|---|
| Herr et al. [1] | 45 | T0–T2, Cis | Median: 5.1 years (range 3–7 years) | OS: 82%<br>Patients with functioning bladder: 67% |
| Herr et al. [2] | 99 | MIBC | Range: 10–20 years | 10 year OS: 76%<br>Recurrence: 34.3%<br>Salvage cystectomy: 18.2% |
| Solsona et al. [3] | 133 | MIBC | 15 years | 5/10/15-year CSS: 81.9%, 79.5%, 76.7%<br>5/10/15-year PFS: 75.5%, 64.9%, 57.8% |

*Cis* Carcinoma in situ, *OS* overall survival, *CSS* cancer-specific survival, *PFS* progression-free survival

### 10.2.1 Baseline Studies on the Effectiveness of Neoadjuvant Chemotherapy

The European Organization for Research and Treatment of Cancer (EORTC) and the Medical Research Council (MRC) conducted a large clinical trial of neoadjuvant chemotherapy in bladder cancer [8].

This study has been reported twice during median follow-up periods of 4 years and 8 years. In the 4-year study, survival rates tended to improve in the neoadjuvant chemotherapy group, but there was no significant difference in survival rates between the groups without neoadjuvant chemotherapy. In median follow-up of 8 years, the risk of death in the neoadjuvant chemotherapy group was found to be statistically significantly reduced by 16%. In addition, the 10-year overall survival rate was 36% versus 30%, and there was a significant difference between the two groups. However, this study only included cisplatin, methotrexate, and vinblastine (CMV), and 40% of patients received radiation therapy instead of radical cystectomy.

Southwest Oncology Group (SWOG) 8710 trial compared three cycles of neoadjuvant MVAC + radical cystectomy versus radical cystectomy alone in bladder cancer [9]. After radical cystectomy, the ratio of pT0 to 38% versus 15% was significantly higher in the neoadjuvant chemotherapy group ($p < 0.001$). Seventy-seven months versus 46 months, median overall survival was higher in neoadjuvant chemotherapy group. The 5-year overall survival rate was 57% versus 43%, which was higher in the neoadjuvant chemotherapy group, but not statistically significant (Table 10.2).

A meta-analysis of the Phase III trial was conducted in 2005 to clarify the effect of neoadjuvant chemotherapy [16]. The study performed a meta-analysis of 11 randomized trials that studied neoadjuvant chemotherapy including SWOG-2810. It was an update to the 2003 meta-analysis of ten randomized trials. This study was categorized and analyzed based on cisplatin alone and cisplatin-based combination chemotherapy. Combination therapy had a significant impact on overall survival (HR = 0.86, 95% CI 0.77–0.95, $p = 0.003$), and disease-free survival (DFS) (HR = rufr0.78, 95% CI 0.71–0.86, $p < 0.0001$)

**Table 10.2** Randomized clinical trials of neoadjuvant chemotherapy in MIBC

| Study | No. of patients | Neoadjuvant arm | Control arm | Stage | Outcomes |
|---|---|---|---|---|---|
| EORTC/MRC [8] | 976 | CMV + RC/RT | RC/RT | T2–4aNxM0 | 10-year OS: 36% vs 30% ($p = 0.037$) |
| Nordic I [10] | 325 | Cisplatin and doxorubicin + RT + RC | RT + RC | T1–4aNxM0 | 5-year OS: 59% vs 51% ($p = 0.1$) |
| Nordic II [11] | 317 | Cisplatin and methotrexate + RC | RC | T2–4aNxM0 | 5-year OS: 53% vs 46% ($p = 0.24$) |
| SWOG [9] | 317 | MVAC + RC | RC | T2–4aN0M0 | 5-year OS: 57% vs 43% ($p = 0.06$) |
| WMURG/ABCSG [12] | 255 | Cisplatin + RT | RT | T2–4aNxMx | No difference |
| GUONE (Bassi et al. [13]) | 206 | MVAC + RC | RC | T2–4aN0M0 | 5-year OS: 55% vs 54% ($p$ = NS) |
| GISTV (Italian Bladder Cancer Study Group, 1996) | 171 | MVE + RC | RC | T2–4N0M0 | Median OS: NR vs 5.5 years ($p$ = NS) |
| CUETO [14] | 122 | Cisplatin + RC | RC | T2–4aNx-2 M0 | 6.5-year OS: 35% vs 37% ($p = 0.95$) |
| Daveca 89-02 [15] | 120 | Cisplatin and methotrexate + RT | RT | T2–4bNx-3 M0 | 5-year OS: 19% vs 24% ($p = 0.98$) |

*CMV* Cisplatin, methotrexate, and vinblastine; *MVAC* methotrexate, vinblastine, doxorubicin, and cisplatin; *MVE* methotrexate, vinblastine, and epirubicin; *OS* overall survival; *RC* radical cystectomy; *RT* radiation therapy; *SWOG* Southwest Oncology Group

**Table 10.3** Meta-analyses of neoadjuvant chemotherapy Phase III trials for MIBC

| Study | No. of trials | No. of patients | Regimen | OS (HR) | DFS (HR) |
|---|---|---|---|---|---|
| Advanced bladder cancer meta-analysis collaboration [17] | 10 | 2688 | Cisplatin-based | 0.87 (0.78_0.98), $p = 0.016$, 5% absolute survival benefit at 5 years | Insufficient data for analysis |
| The Cancer Care Ontario program in evidence-based care practice guidelines initiative [18] | 11 | 2605 | Cisplatin-based | 0.90 (0.82_0.99), $p = 0.002$ | Insufficient data for analysis |
| Advanced bladder cancer meta-analysis collaboration [16] | 11 | 3005 | Cisplatin-based | 0.86 (0.77_0.95), $p = 0.003$, 5% absolute survival benefit at 5 years | 0.78 (0.71_0.86), $p < 0.0001$ |

*OS* overall survival, *DFS* disease-free survival

also had a significant effect. The 5-year survival rate was improved from 45 to 50% [17] (Table 10.3).

As a result of these clinical trials and meta-analysis, cisplatin-based neoadjuvant chemotherapy seems to have an overall survival improvement of 5–6% and a pathologic complete remission of 30–40%.

## 10.2.2 Target Group of Neoadjuvant Chemotherapy

National Comprehensive Cancer Network (NCCN) guideline [19]

- cT2N0M0: strongly consider neoadjuvant chemotherapy
- cT3–4aN0M0: recommends cisplatin-based neoadjuvant chemotherapy

European Association of Urology (EAU) guideline [20]

- T2–4aN0M0: recommend cisplatin-based neoadjuvant chemotherapy

## 10.2.3 Regimens of Neoadjuvant Chemotherapy

DDMVAC has proven to be more effective in advanced bladder cancer than conventional MVAC. It is also possible that the patient will be better able to tolerate chemotherapy by administering growth factors together [9, 21, 22]. In a multicenter prospective, Phase II study in patients with cT2–4aN0–1 M0, neoadjuvant DDMVAC had grade 1–2 nephrotoxicity but no nephrotoxicity at grade 3–4 [21]. There were no deaths due to nephrotoxicity. And 49% of patients showed pathologic downstaging. Other bevacizumab and DDMVAC neoadjuvant clinical trials reported a 5-year overall survival of 63% and a 5-year disease-specific survival of 64%. Pathologic downstaging showed similar results with pT0N0 of 38% and pT1N0 of 53% [22].

- DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for three or four cycles (Table 10.4)
- Gemcitabine and cisplatin for four cycles (Table 10.4)
- CMV (cisplatin, methotrexate, and vinblastine) for three cycles (Table 10.4)

## 10.2.4 Predictors and Risk Factors of Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy in all patients does not show good results. It is important to selectively administer the benefit to the patient. Several factors that can be used to predict such a good outcome have been studied. These are signs of suspected locally advanced disease states:

**Table 10.4** Regimens of neoadjuvant chemotherapy

| Regimen | Dosing |
|---|---|
| Dose-dense methotrexate + vinblastine + doxorubicin + cisplatin (DDMVAC) with growth factor support [9, 21] | Day 1: methotrexate 30 mg/m$^2$ IV |
| | Day 2: vinblastine 3 mg/m$^2$ IV, plus doxorubicin 30 mg/m$^2$ IV, plus cisplatin 70 mg/m$^2$ IV |
| | Day 4: granulocyte colony-stimulating factor (G-CSF) 240 µg/m$^2$ subcutaneous (SQ) injection for 7 consecutive days (days 4 through 10). May be extended for up to a total of 14 consecutive days |
| | Repeat every 2 weeks for 3–4 cycles |
| Gemcitabine + cisplatin (GC) [23–25] | Days 1, 8, and 15: gemcitabine 1000 mg/m$^2$ IV over 30–60 min |
| | Day 2: cisplatin 70 mg/m$^2$ |
| | Repeat every 4 weeks for 4 cycles |
| Cisplatin + methotrexate + vinblastine (CMV) [16] | Day 1: methotrexate 30 mg/m$^2$ IV bolus plus vinblastine 4 mg/m$^2$ IV bolus |
| | Day 2: cisplatin 100 mg/m$^2$ IV infusion; followed by hydration; followed by leucovorin 15 mg orally or IV every 6 h for 4 doses (commencing 24 h after methotrexate on day 1) |
| | Day 8: methotrexate 30 mg/m$^2$ IV bolus plus vinblastine 4 mg/m$^2$ IV bolus |
| | Day 9: leucovorin 15 mg orally every 6 h for 4 doses after methotrexate on day 8 |
| | Repeat every 3 weeks for 3 cycles |

bladder mass palpated by bimanual examination, extravesical extension findings or local organ involvement confirmed by imaging studies (cT3/T4), hydronephrosis, lymphovascular invasion (LVI), and variant histology on histologic examination [26–29]. In the SWOG-8710 study, the response rate of neoadjuvant chemotherapy varied according to the clinical stage. After neoadjuvant chemotherapy, stage was down in 55% of cT2 patients and in 35% of T3/4 patients [30]. The postoperative pT0 ratio was also related to the clinical stage. The pT0 ratio was 39% in cT2 and 24% in cT3/4 [30].

Hydronephrosis is known to be associated with invasive disease. The risk is increased in bilateral involvement rather than unilateral [31]. And hydronephrosis is an independent factor that can predict oncologic outcomes such as recurrence-free survival [32]. LVI is an independent poor predictor of OS, DSS, and local and distant recurrence. The variant histology of bladder cancer has various subtypes. However, the subtypes associated with early metastasis are small cell, micropapillary, neuroendocrine, and plasmacytoid [33, 34]. In the case of micropapillary type, the frequency of extravesical and metastasis is high, and it is reported to be associated with poor OS [33, 34]. Small cell and neuroendocrine types are known to have poor prognosis. It is also known to be related to poor OS [35]. Plasmacytoid type has a poor prognosis and is known to be associated with early recurrence and peritoneal metastasis [36, 37].

## 10.3 Adjuvant Chemotherapy

Adjuvant chemotherapy aims to increase survival by treating microinvasion in high-risk patients who are likely to fail after radical cystectomy. There have been many studies, but the effect of adjuvant chemotherapy has not been clearly demonstrated. However, adjuvant chemotherapy has several advantages over neoadjuvant chemotherapy. First, there is no delay in treatment. It is possible to perform local treatment through immediate radical cystectomy and also possible to avoid treatment delays in patients who do not respond well to chemotherapy. Second, the final pathologic results suggest that patients who are likely to benefit from chemotherapy may be selected, taking into account the side effects of chemotherapy and the benefits of treatment.

### 10.3.1 Baseline Studies on the Effectiveness of Adjuvant Chemotherapy

The first prospective randomized clinical trial demonstrating the benefit of survival for adjuvant chemotherapy was reported by the Southern California group [38]. This study was a cisplatin-based combination chemotherapy study in patients with pathologic T3–T4 and N positive after radical cystectomy. Three-year overall survival and disease-free survival were analyzed, and the median survival was significantly improved in the adjuvant chemotherapy group. The 3-year disease-free survival was 70% versus 46% ($p = 0.001$), overall survival was 71% versus 50% ($p = 0.027$), and median survival improved to 4.3 years versus 2.4 years ($p = 0.0062$). However, there is a disadvantage that the number of patients is low and the chemotherapy regimen is not standardized. There have been many studies of adjuvant chemotherapy trials since then, but most studies have failed to yield significant results. In 2010, the Spanish Oncology Genitourinary Group's SOGUG 99/01 trial performed four cycles of adjuvant paclitaxel, cisplatin, and gemcitabine in patients with T3–T4 and N positive. Median follow-up was 30 months, and 5-year overall survival was 60% versus 31% ($p = 0.009$), which was significantly improved in adjuvant chemotherapy group [39].

Recently, the results of the clinical trials of the Italian multicenter randomized trial and the EORTC 30994 trial were published [40, 41]. Two studies were performed on T2G3, T3–T4, and N-positive patients. Gemcitabine, cisplatin, gemcitabine, cisplatin, and high-dose MVAC were used for adjuvant chemotherapy. The medial follow-up was 35 months and 84 months, respectively. Both studies showed no significant improvement in the 5-year overall survival and disease-free survival.

Sternberg and Collette conducted a meta-analysis study, including six randomized clinical trials about adjuvant chemotherapy [42]. In this study, patients with adjuvant chemotherapy had a 3-year overall survival improvement of 9% (HR 0.75, 95% CI 0.60–0.96, $p = 0.019$) over the control group [42]. Despite these positive results, the efficacy of adjuvant chemotherapy is not clearly demonstrated and has a limited evidence (Table 10.5).

### 10.3.2 Target Group of Adjuvant Chemotherapy

National Comprehensive Cancer Network (NCCN) guideline [19]

- T2–4 node positive: recommends cisplatin-based neoadjuvant chemotherapy

European Association of Urology (EAU) guideline [20]

- T3–4 node positive: recommends cisplatin-based neoadjuvant chemotherapy

### 10.3.3 Regimens of Adjuvant Chemotherapy

Regimens of adjuvant chemotherapy are the same as neoadjuvant chemotherapy.

## 10.4 Adjuvant Radiotherpay

Local recurrence of pT3 patients after radical cystectomy is a serious problem. Several prospective studies have reported the difficulty of reducing the risk of local recurrence with chemotherapy alone. In recent clinical trials at the Egyptian National Cancer Institute, chemotherapy plus radiotherapy was more effective than chemotherapy alone in reducing local recurrence rate and increasing DFS and OS in acceptable toxicity. There has been progress in the role of adjuvant RT for local-regional control after bladder resection, but there is still disagreement about the role of radiation therapy [52].

**Table 10.5** Randomized clinical trials of adjuvant chemotherapy in MIBC

| Study | No. of patients | | Neoadjuvant arm | Stage | Outcomes | |
|---|---|---|---|---|---|---|
| | Adjuvant | Control | | | DFS (AC vs CT) | OS (AC vs CT) |
| Logothetis et al. [43] | 71 | 268 | CISCA | T3–4N1 | 2 year DFS: 70% vs 30% ($p = 0.00012$) | |
| Bono et al. [44] | 35 | 48 | Cisplatin + methotrexate | T2–4aN0M0 | 51% vs 56% ($p = 0.663$) | 51% vs 62% ($p = 0.313$) |
| Skinner et al. [38] | 44 | 47 | CAP | T3–4N+M0 | 3-year DFS: 70% vs 46% ($p < 0.001$) | 3-year OS: 71% vs 50% ($p = 0.027$) |
| Stockle et al. [45] | 26 | 23 | MVEC | T3b–4a | 3-year DFS: 66% vs 15% ($p = 0.021$) | 3-yr OS: 58% vs 15% ($p = 0.048$) |
| Studer et al. [46] | 37 | 40 | Cisplatin | T1G2–4a | N/A | 57% vs 54% ($p = 0.877$) |
| Freiha et al. [47] | 25 | 25 | CMV | T3b–4 | 37 months vs 12 months ($p = 0.002$) | 63 months vs 36 months ($p = 0.152$) |
| Otto et al. [48] | 55 | 53 | MVAC | T3N1–2M0 | 4-year DFS: 44% vs 40% | |
| Lehmann et al. [49] | 26 | 23 | MVEC | T3–4aN+ | 10-year DFS: 43.7% vs 13.0% ($p = 0.002$) | 10-year OS: 26.9% vs 17.4% ($p = 0.069$) |
| Paz-Ares et al. (SOGUG 99/01), [50] | 68 | 74 | Paclitaxel + GC | T3–4N+ | N/A | 60% vs 31% ($p < 0.0009$) |
| Stadler et al. [51] | 58 | 56 | MVAC | T1–2(p53+) | N/A | Almost 40% ($p = 0.89$) |
| Cognetti et al. [40] | 102 | 92 | GC | T2G3;<br>T3–4N+ | 5-year DFS: 37.2% vs 42.3% ($p = 0.70$) | 5-year OS: 43.4% vs 53.7% ($p = 0.24$) |
| Sternberg et al. [41] (EORTC 30994) | 141 | 143 | GC, MVAC | T3–4N+ | 5-year DFS: 47.6% vs 31.8% ($p < 0.0001$) | 5-year OS: 53.6% vs 47.7% ($p = 0.13$) |

*CAP* cisplatin, cyclophosphamide, and doxorubicin; *CISCA* cisplatin, cyclophosphamide, and doxorubicin (Adriamycin); *CMV* cisplatin, methotrexate, and vinblastine; *GC* gemcitabine and cisplatin; *MVAC* methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin; *MVEC* methotrexate, vinblastine, epirubicin, and cisplatin

### 10.4.1 Baseline Studies on the Effectiveness of Adjuvant Radiotherapy

It has been reported that adjuvant radiation therapy reduces locoregional recurrence and improves disease-free survival and overall survival compared to radical cystectomy alone (Table 10.6).

However, adjuvant radiation therapy was not noticed due to excessive gastrointestinal (GI) toxicity.

Early studies showed late GI toxicity in 36% of patients treated with standard fraction 10% of patients treated with hyper-fractionation. And severe late toxicity at 50% after sandwich radiation therapy. In the early studies, high rates of toxicity included factors such as older 2-D radiation therapy, whole pelvic field large radiotherapy, and AP/PA beam use to increase bowel dose. Recent reported clinical trials using 3-D conformal radiotherapy showed a low late GI toxicity of 7% [54].

### 10.4.2 Target and Radiation Dose of Adjuvant Radiotherapy

Based on pathologic findings, suspicious sites of residual tumor are included, including inguinal lymph nodes and pelvic lymph nodes.

- Suspicious sites of microscopic residual tumor: 45–50.4 Gy EBRT
- Resection margin involvement: 54–60 Gy EBRT

**Table 10.6** Randomized clinical trials of adjuvant radiotherapy in MIBC

| Study | No. of patients | Stage | Protocol | Outcomes |
|---|---|---|---|---|
| Zaghloul et al. [53] | 236 | pT3a–4a | Conventional arm<br>37.5 Gy/10 Fs/2 weeks<br>Hyper-fractionation arm<br>50 Gy/25 Fs/5 weeks<br>Observation arm | 5-year DFS:44% vs 49 vs 25% ($p < 0.01$)<br>LRC: 98% vs 87% vs 50% ($p < 0.01$) |
| El-Monim et al. [54] | 100 | pT2b–3a | Pre-op/post-op double arm<br>50 Gy/25 Fs/5 weeks | 3-year OS: 53.4% vs 51.8%<br>3-year DFS: 47.4% vs 34.1%<br>3-year LRC: 89.3% vs 80.6%<br>3-year MFS: 61.5% vs 55.7% |
| Zaghloul et al. [52] | 120 | ≥pT3b or N+ | CTx + RT/CTx<br>CTx + RT: GC two cycles + 45 Gy/15 Fs/3 weeks + : GC two cycles<br>CTx: GC two cycles | 2-year LRFS: 96% vs 69% ($p < 0.01$)<br>2-year OS: 71% vs 60% ($p = 0.11$)<br>2-year DFS: 68% vs 56% ($p = 0.07$) |

*LRC* locoregional control; *MFS* metastases-free survival; *DRFS* local-regional recurrence-free survival; *GC* gemcitabine/cisplatin; *RT* radiotherapy; *CTx* chemotherapy

- Extranodal extension: 54–60 Gy EBRT
- Gross residual tumor: 66 to 70 Gy EBRT

## 10.5 Radical Cystectomy

Radical cystectomy and bilateral pelvic lymph node dissection are standard surgical treatment methods for MIBC. Radical cystectomy can help to reduce effective local control and pelvic recurrence rates. Men usually perform hysterectomy and cystectomy in women with cystoprostatectomy. The man is excised including the bladder and adjacent prostate, seminal vesicle, proximal vas deference, and distal ureter. And the woman is excised including the bladder, urethra, vagina, uterus, fallopian tubes, ovaries, and distal ureter. In the treatment of high-risk NMIBC bladder cancer, the accuracy of the TURB results is appropriate; however, understaging is also frequent. For this reason, pelvic lymph node dissection is considered an essential part of radical cystectomy.

### 10.5.1 Indications for Radical Cystectomy

National Comprehensive Cancer Network (NCCN) guideline [19]

- T2-T4aN0M0
- T1/high grade or T2 at re-TURBT
- NMIBC with incomplete response to intravesical BCG or agent

European Association of Urology (EAU) guideline [20]

- T2-T4aN0M0
- T1 with the highest risk progression tumor
  - T1G3/high grade + CIS
  - Multiple or large (>3 cm) T1G3/high grade
  - Recurrent T1G3/high grade
  - T1G3/high grade + CIS in the prostatic urethra
  - Lymphovascular invasion
  - BCG-refractory tumors
  - Extensive papillary disease cannot be regulated by intravesical treatment and TURB

### 10.5.2 Timing of Radical Cystectomy

In studies comparing primary MIBC patients with patients who progressed to MIBC at NMIBC, patients who progressed to MIBC at NMIBC had a worse prognosis than those with primary MIBC [55]. In another study, high-risk NMIBC patients reported that death and progression to MIBC occurred within 2 years of diagnosis. The study also reported that the progression rate to MIBC and mortality rate of high NMIBC patients were approximately 20% and 15%, respectively [56].

There is a study on oncological outcomes according to the time of radical cystectomy after diagnosis of MIBC. This study reported a case of delayed cystectomy over 3 months after diagnosis of MIBC [57]. Especially, T2 tumors showed a statistically significant survival rate when operated within 3 months after diagnosis of cystectomy. Since then, several studies have reported that disease-specific survival and overall survival worsened in patients who underwent radical cystectomy for more than 3 months after initial diagnosis [58–60]. In a study comparing tumor upstaging and lymph node metastasis in patients undergoing radical cystectomy before and after 3 months, the rate of upstaging and lymph node metastasis was higher in patients with delayed surgery [61]. These studies may indirectly indicate that aggressive treatment is needed immediately after the diagnosis of MIBC patients.

### 10.5.3 Stage Evaluation

Clinical stage evaluation: contrast computer tomographic (CT) chest, CT abdomen-pelvis scan, and bone scan tests are required for clinical stage evaluation (Figs. 10.1, 10.2, 10.3, and 10.4).

Imaging studies are very important in stage workup of bladder cancer. However, there is a difference in accuracy between test methods, and the accuracy is not perfect. CT has limited usefulness in bladder cancer. The accuracy is relatively low (49–55%) [62]. In addition, it has high interobserver variability [63] (Fig. 10.5).

MRI is more accurate than CT (62–63%) and has a high interobserver agreement. It can distinguish locally advanced disease from organ-confined states (82–90%) [64, 65] (Table 10.5).

CT and MRI are widely used for imaging of lymph node status (Fig. 10.6). However, these imaging tools are less accurate. It is difficult to confirm pathologic state or metastasis by the morphological appearance of node on the image studies [64–66]. Approximately 25% of patients with node-positive postoperative pathologic findings were found to be node negative in preoperative imaging studies [64–66].

To complement these imaging studies, one of the methods we use is radioisotope-based test. The PET or PET-CT allows for the examination of metabolic processes such as membrane metabolism or proliferation rate for morphologically normal nodes. 18F-fluorodeoxyglucose (FDG) and 11C-choline are the most commonly used radiotracers. However, these PET-based tests do

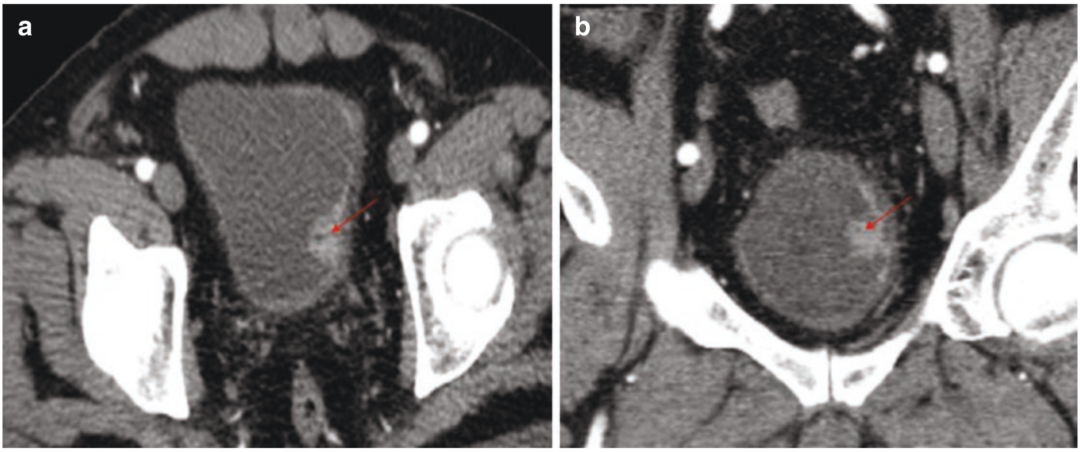

**Fig. 10.1** Muscle-invasive bladder cancer contrast-enhanced CT image shows a papillary mass (arrow) in the left lateral aspect of the bladder: (**a**) axial view, (**b**) coronal view

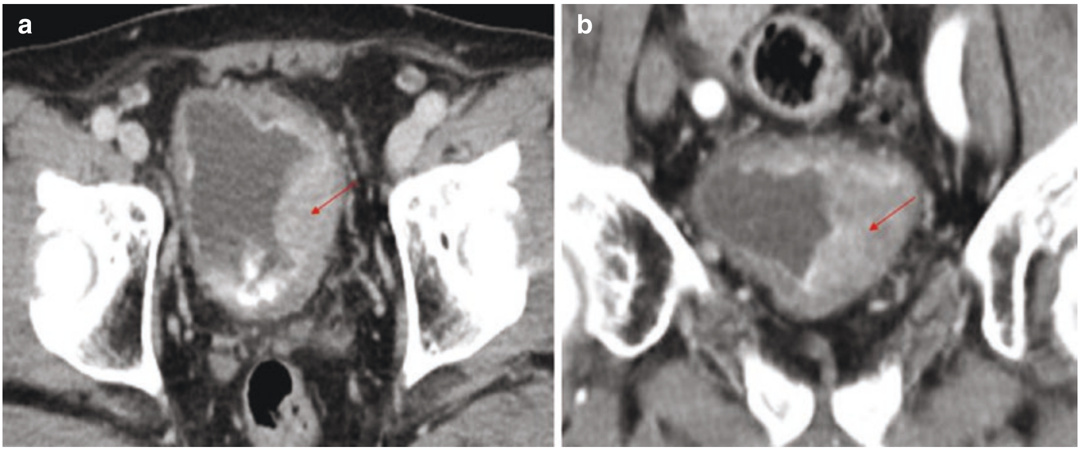

**Fig. 10.2** Muscle-invasive bladder cancer contrast-enhanced CT image shows a broad-based mass (arrow) in the left posterolateral aspect of the bladder with tumor spread in the perivesical fat: (**a**) axial view, (**b**) coronal view

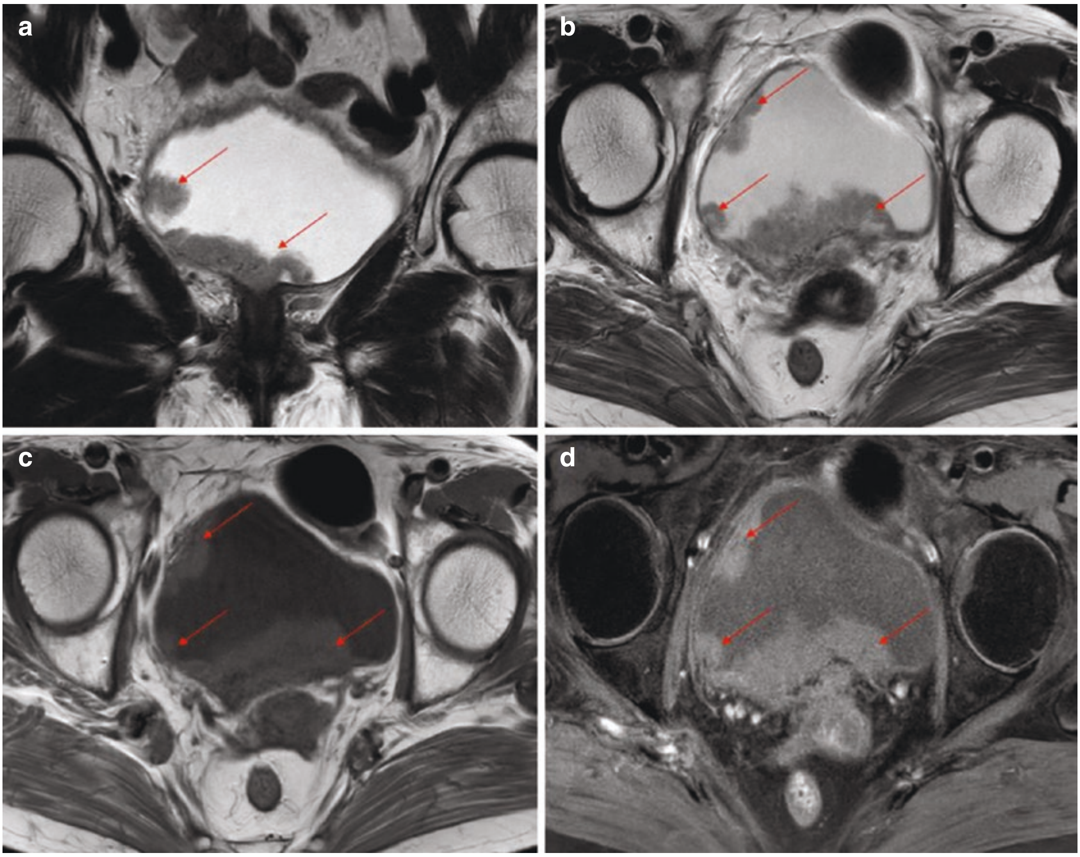

**Fig. 10.3** Muscle-invasive bladder cancer contrast-enhanced MRI image shows a multiple mass (arrow) in the right lateral and posterior aspect of the bladder: (**a**) T2-weighted MR axial, (**b**) T2-weighted MR coronal, and (**c**, **d**) T1-weighted MR images

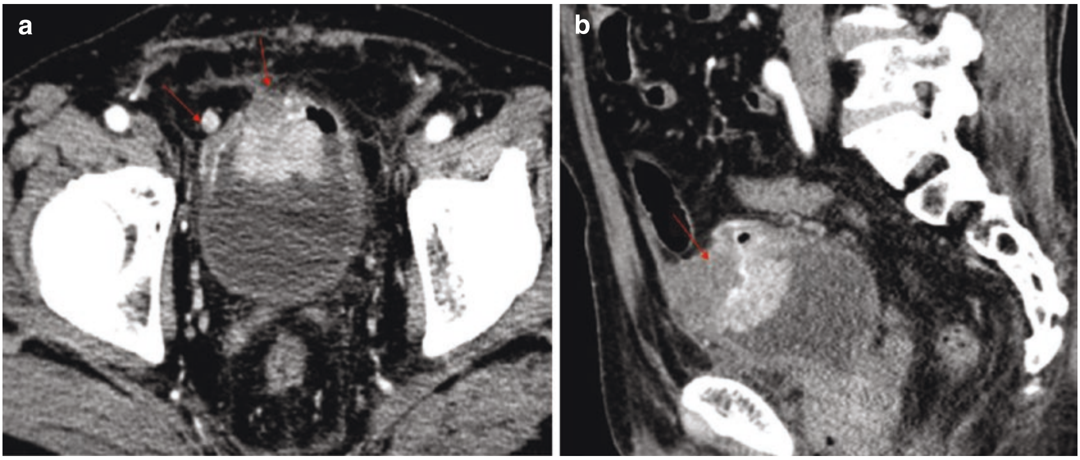

**Fig. 10.4** Muscle-invasive bladder cancer contrast-enhanced CT image shows a papillary mass (arrow) in the anterior aspect of the bladder with extravesical extension: (**a**) axial view, (**b**) sagittal view

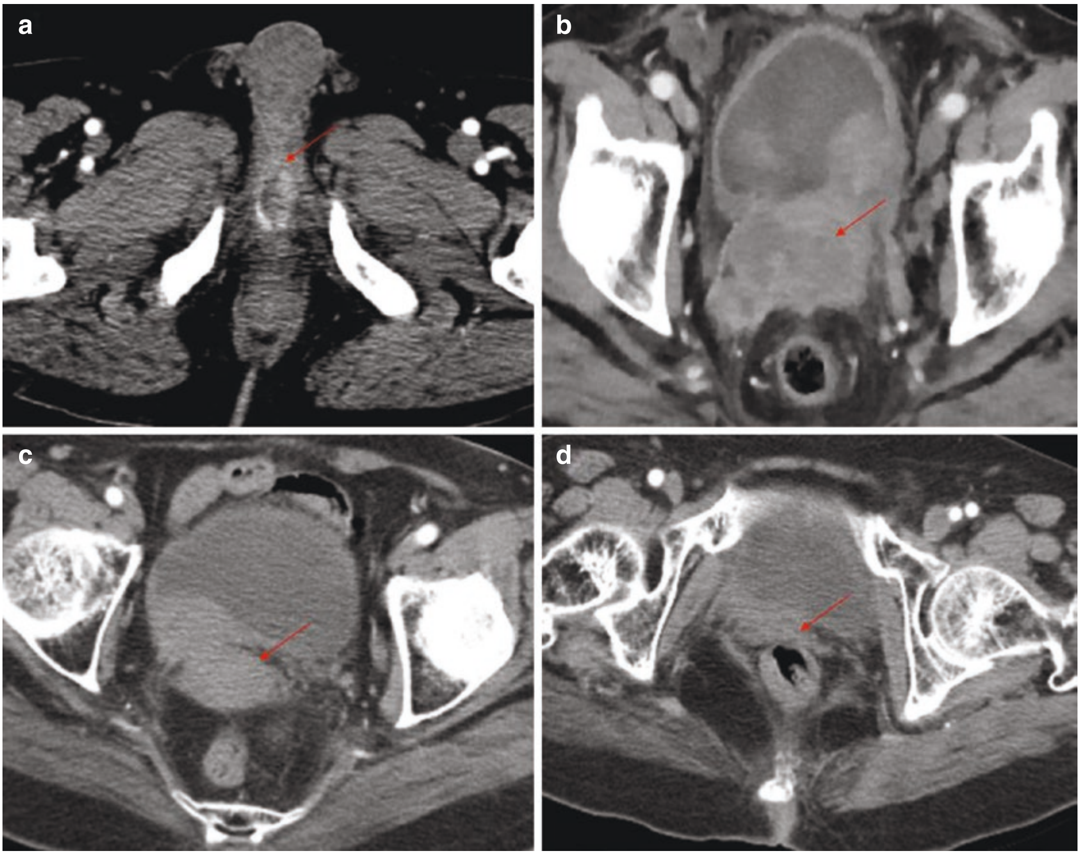

**Fig. 10.5** Muscle-invasive bladder cancer contrast-enhanced CT image shows (**a**) urethra invasion, (**b**) prostate invasion, (**c**) uterus invasion, and (**d**) vagina invasion

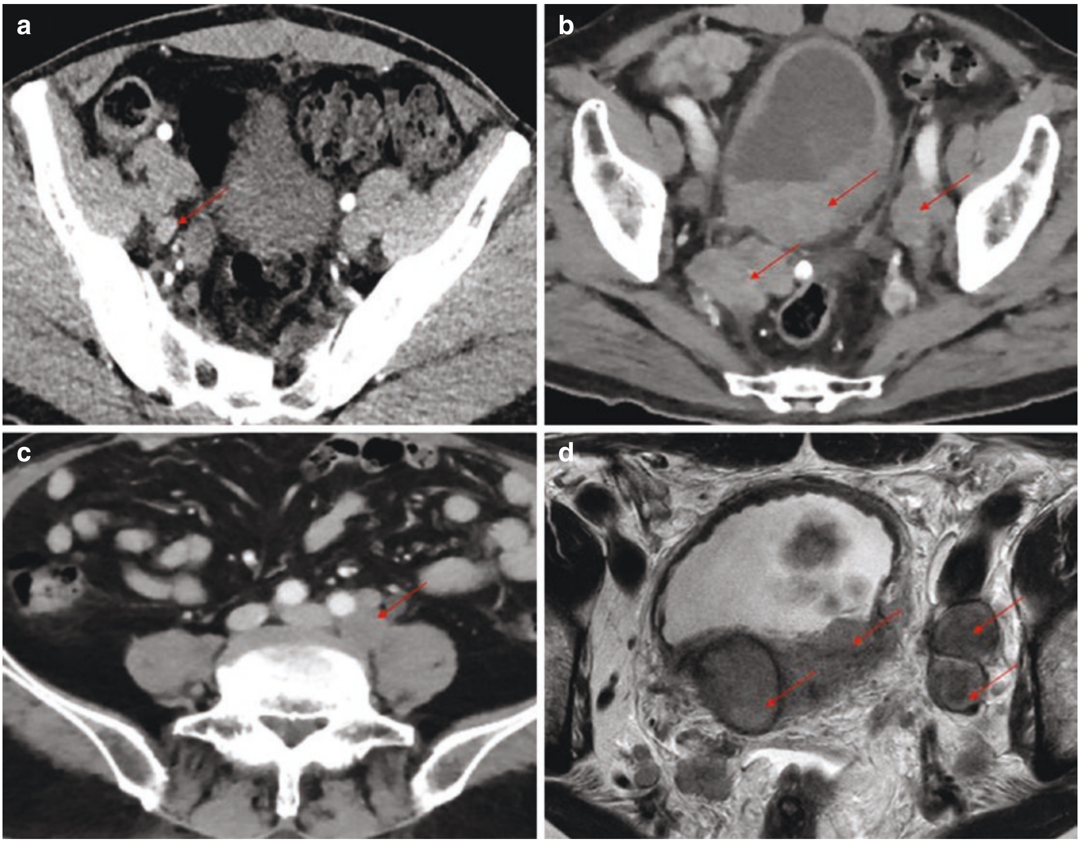

**Fig. 10.6** Metastatic bladder cancer with contrast-enhanced CT image shows (**a**) right internal iliac single lymph node metastasis, (**b**) multiple lymph node metastasis, (**c**) left common iliac lymph node metastasis, and (**d**) multiple lymph node metastasis in T2-weighted MR axial view

not detect small metastases or microscopic metastases [66] (Fig. 10.7).

## 10.5.4 Preoperative Preparation

### 10.5.4.1 Thromboembolic Prophylaxis

The incidence of symptomatic venous thromboembolism (VTE) after RC is 3–11%. And the incidence varies according to the risk group [67] (Table 10.7).

Neoadjuvant chemotherapy before RC can increase the risk of VTE [69]. Zareba et al. found that 19.1% of NAC patients developed VTE (RR3.39 95% CI 1.39–8.24). The overall incidence of VTE in RC patients, including NAC patients, was 8.4% [70]. There was also a difference in the timing at which VTE occurred. Most of the NAC patients had VTE events prior to surgery, but RC patients without NAC had postoperative VTE event [70].

In another study of 761 patients who underwent RC with NAC, the incidence of VTE was 14% and occurred in 58% of patients before surgery. NAC ($p = 0.01$) was an independent predictor of VTE development [71]. However, despite these high VTE ratios, NAC has been reported not to increase patient mortality [71].

For patients receiving RC, thromboembolic prophylaxis using low-molecular-weight heparin injection 12 h before surgery or 6–8 h after surgery or compression stockings or intermittent mechanical air compression stockings are recommended [72, 73].

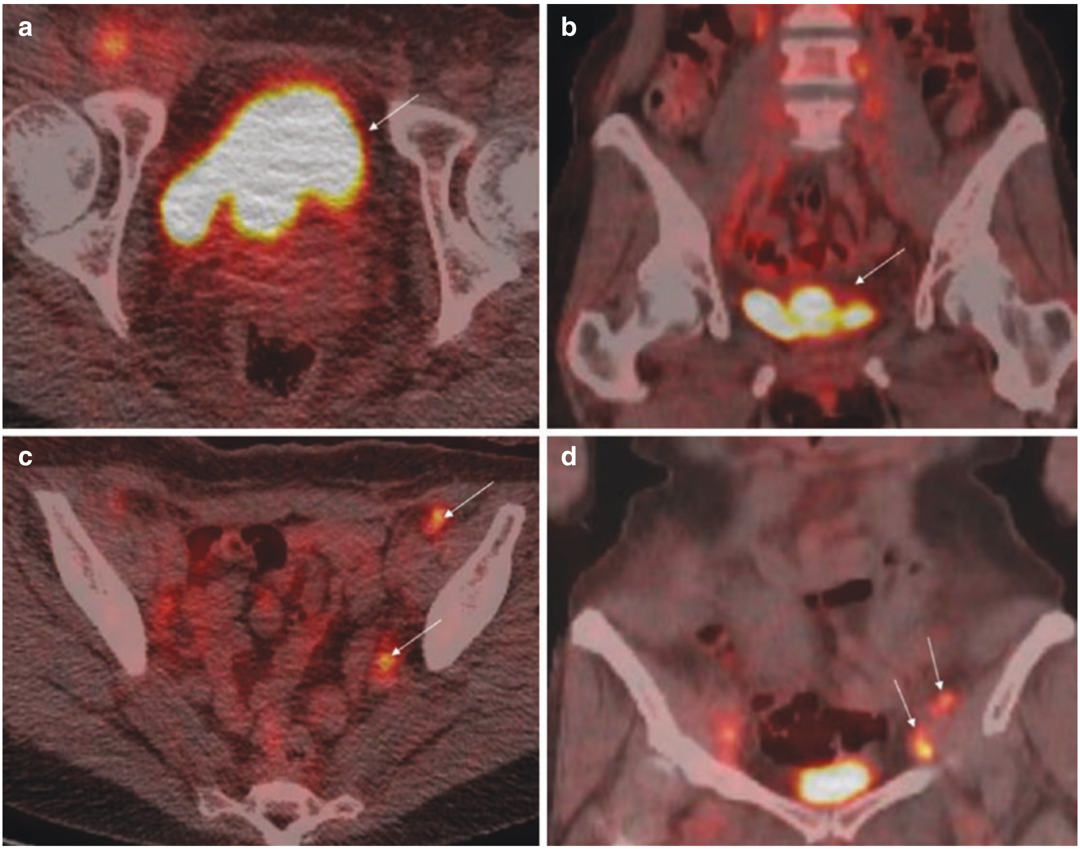

**Fig. 10.7** Muscle-invasive bladder cancer F-18 FDG PET image shows a hypermetabolic mass in the bladder (**a**) axial view, (**b**) coronal view and left retroperitoneal lymph nodes (**c**) axial view, (**d**) coronal view

**Table 10.7** Risk classification and AUA recommendation for venous thromboembolism (VTE) [68]

| Risk of venous thromboembolism (VTE) | AUA recommendation |
|---|---|
| Low risk (minor surgery, <40 years, no risk factors) | No prophylaxis |
| Moderate risk (40–60 years, or minor surgery with risk factors) | Pharmacological or pneumatic mechanical prophylaxis |
| High risk (>60 years, or 40–60 years with risk factors) | Pharmacological or pneumatic mechanical prophylaxis |
| Very high risk (presence of multiple risk factors) | Pharmacological and pneumatic mechanical prophylaxis |

| | |
|---|---|
| Risk factor of VTE | Surgery; trauma of major or lower extremity; immobility; paresis; malignancy; cancer therapy (hormonal, chemotherapy or radiotherapy); previous VTE; increasing age; pregnancy and the postpartum period; estrogen-containing oral contraception or hormone replacement therapy; selective estrogen receptor modulators; acute medical illness; heart or respiratory failure; inflammatory bowel disease; nephrotic syndrome; myeloproliferative disorders; paroxysmal nocturnal hemoglobinuria; obesity; smoking; varicose veins; central venous catheterization; and inherited or acquired thrombophilia |

Patients with increased venous thromboembolism risk are advised to continue thromboembolic prophylaxis for up to 4 weeks after rectal and pelvic surgery [74, 75].

#### 10.5.4.2 Antimicrobial Prophylaxis

The guidelines recommend prevention of aerobic and anaerobic pathogens. Second- or third-generation cephalosporin is recommended.

Intravenous antibiotics should be administered within 1 h of surgical incision [76].

#### 10.5.4.3 Stoma Marking

Careful marking of the ostomy site to avoid interference, both in a standing and in a seated position, is performed to maximize appliance fit and to minimize stomal irritation [77] (Fig. 10.8).

#### 10.5.4.4 Preoperative Bowel Preparation

Traditionally bowel preparation is needed because of the urinary diversion performed by cutting a part of the intestine. However, there is the early recovery after surgery (ERAS) protocol, which claims that bowel preparation is not necessary for early recovery (Table 10.8).

#### 10.5.4.5 Transfusion

The blood transfusion rate after RC is about 30% [78]. Considering the immunosuppressive effect of transfusion, there have been many studies on the effect of transfusion on the oncological outcome [78, 79]. These studies report that transfusion itself is directly related to OS, CSS, and RFS, as well as the complexity of disease and surgery in patients receiving transfusions [78, 79]. If there is a possibility of transfusion or anemia, iron supplementation should be used [80, 81]. It is recommended that iron supplementation be used in patients with possible transfusions or in patients with anemia. In the case of transfusion, it is better to avoid cell saver or autologous transfusion to avoid transferring metastatic cells [80, 81].

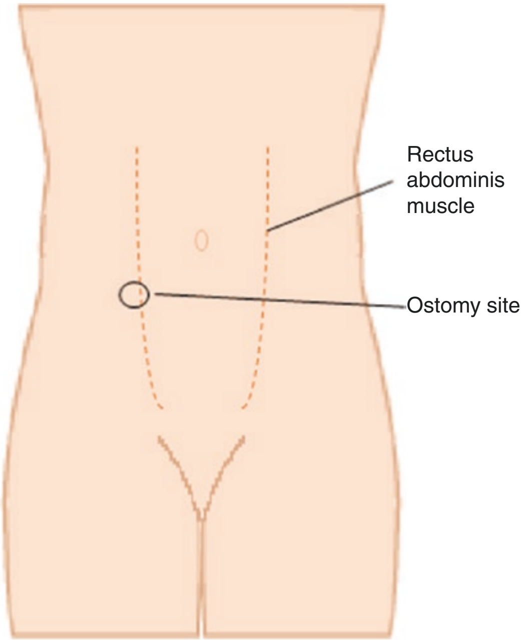

**Fig. 10.8** Location of the ostomy site

**Table 10.8** Preoperative bowel preparation (Seoul National University Hospital)

| | |
|---|---|
| Pre-op day 2 | |
| | Sips of water |
| | Intravenous hydration (DNK 2 L + plasma solution 1 L 120 mL/h) |
| | CoolPrep 2 L powder for solution |
| | Bisacodyl 2 sup insertion to the anus |
| Pre-op day 1 | |
| | Sips of water |
| | Intravenous hydration (DNK 2 L + plasma solution 1 L 120 mL/h) |
| | CoolPrep 2 L powder for solution |
| | Glycerin enema rectal × 2 |
| | Bisacodyl 2 sup insertion to the anus |
| OP day | |
| | Nothing by mouth |
| | Plasma solution 1 L 80 mL/h |
| | 2nd Cepa + metronidazole intravenous injection |

*DNK* Dextrose 5%/Na/K, *Cepa* Cephalosporin

#### 10.5.4.6 Nasogastric Tube Insertion

Early removal of NG tubes after major abdominal surgery has Level 1 evidence [82]. There was no correlation between the time of removal of the NG tube and postoperative ileus and length of hospital stay in RCT for RC patients [83].

### 10.5.5 Enhanced Recovery After Surgery (ERAS)

The first ERAS guideline was published in 2013. Most were extrapolated from colorectal surgery [84]. There were several prospective studies, but none of the 22 components of the ERAS guideline was included. These studies have limitations such as lack of randomized control studies, small study numbers, and different protocols and endpoints. However, even with these limitations and volatility, ERAS has a positive impact on patient recovery [85].

#### 10.5.5.1 Preoperative Carbohydrate Loading

Preoperative bowel preparation causes electrolyte problems in patients and is now reported to be rather bad [86]. In a review of 18 RCT studies, we showed that there was no difference between groups with mechanical bowel preparation and groups with rectal enema and without bowel preparation [87]. Preoperative bowel preparation also had no benefit in reconstruction with ileal conduit or small-bowel neobladder [88, 89].

The European Anesthesia Guidelines state that solid food is available up to 6 h before surgery and clear liquid food is available up to 2 h before surgery [90]. Carbohydrate loading is one of the standardized methods of ERAS. Surgery leads to the development of transient insulin resistance. It induces a physiological state similar to type 2 diabetes during postoperative recovery [91]. The severity of surgery is proportional to the physiological state, and the severity of the surgery is greater, the degree of insulin resistance is greater, and it takes time to recover to normal [91]. ERAS recommends carbohydrates to be loaded for 2 h before surgery, reducing anxiety and thirst, reducing protein and nitrogen losses, and reducing insulin resistance [92, 93]. It also preserves body mass and strength and shortens the length of stay in the hospital [94].

#### 10.5.5.2 Perioperative/Postoperative Anesthesia

An important principle of using anesthetics in EARS is the use of appropriate analgesics to minimize nausea and vomiting after surgery and minimize opiate use. During surgery, anesthesia inducers are short-acting agents such as propofol, rather than long-acting benzodiazepines, and alfentanil or remifentanil is preferred as analgesic [95]. Opioid-sparing analgesics accelerate bowel recovery and reduce bowel obstruction after surgery [95]. Epidural analgesia reduces postoperative stress response, promotes functional recovery, reduces cardiopulmonary complications, and improves analgesia [96].

It is recommended that thoracic insertion of T10 level and low doses of fentanyl, morphine, and bupivacaine be given to patients undergoing pelvic surgery and that chest EDA maintained for 72 h after cystectomy [95].

Alvimopan is a peripherally active μ-opioid receptor antagonist. Alvimopan helps the patient to tolerate a hard diet and helps to shorten the length of recovery time for patients who have undergone colorectal surgery [97]. RCT comparing alvimopan with placebo reported that the use of alvimopan improved post-op gastrointestinal recovery and hospital stay [77].

#### 10.5.5.3 Early Oral Diet

In colorectal resection patients, early oral diets have been reported to reduce the length of the first bowel movement and reduce hospital stay [98]. It is also reported that there is no increase in complications due to early oral feeding. Early oral diets are helpful in the recovery of muscle function and wound healing and in reducing postoperative sepsis. It also helps to reduce insulin resistance due to fasting during surgery [99].

#### 10.5.5.4 Early Mobilization

The effects of early mobilization on the improvement of ERAS results are still insufficient (Pang et al.). Of the patients, the early mobilization after RC reduced the hospitalization period and reduced the rehospitalization due to postoperative complications [100]. In addition, early mobilization also reduces the risk of pulmonary complications and thromboembolism [101]. (Fig. 10.9).

### 10.5.6 Open Radical Cystectomy: Male

#### 10.5.6.1 Procedure

Position: supine position 15° flexed

Incision: low midline incision extended above the umbilicus (from 2 cm above the umbilicus to above the symphysis pubis) (Fig. 10.10)

1. Mobilization and division of the umbilicus.
   Both sides of the bladder are separated from the pelvic side wall. The medial umbilical ligaments are incised to the level of the internal inguinal rings on both sides and approach the retroperitoneum (Fig. 10.11).
2. Looking for bilateral ureters and ureter dissection.
   The peritoneum is incised along the external and common iliac vessels. The ureter crosses the common iliac artery and enters the bladder. After the ureter is dissected and cut at a position close to the bladder, a frozen section analysis of the distal tip of the cut ureter is performed (Fig. 10.12).

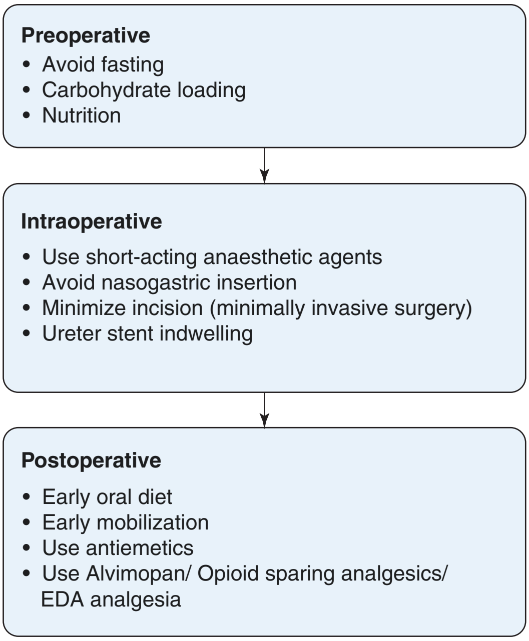
Preoperative
• Avoid fasting
• Carbohydrate loading
• Nutrition
Intraoperative
• Use short-acting anaesthetic agents
• Avoid nasogastric insertion
• Minimize incision (minimally invasive surgery)
• Ureter stent indwelling
Postoperative
• Early oral diet
• Early mobilization
• Use antiemetics
• Use Alvimopan/ Opioid sparing analgesics/ EDA analgesia

**Fig. 10.9** Enhanced recovery after surgery (ERAS)

3. Endopelvic fascia incision and dorsal venous complex division.
   Endopelvic fascia is excised and DVC ligation is performed like prostatectomy (Fig. 10.13).
4. Bilateral lateral pedicle of the bladder is ligated using energy device or GIA (Fig. 10.14).
5. Bilateral posterior pedicle of the bladder is ligated using energy device or GIA.
   Find the plane between the rectum and the bladder. Anterior traction of the bladder exposes the pouch of Douglas. The bladder and prostate posterior pedicle are ligated using energy device or GIA along Denonvillier's space (Fig. 10.15).
6. Removal of the bladder.
   The bladder is removed after resection of the urethra. When removing the bladder, the man removes the prostate and seminal vesical together. Women remove most of uterus, ovaries, and vagina together.

#### 10.5.6.2 Sexual Function-Preserving Cystectomy

Patients with T3, node-positive, and poorly differentiated tumors showed a short survival rate as expected in several studies on sexual function-preserving cystectomy [102, 103]. It is thought that the poor cancer control is caused by underestimating the clinical disease status. Sexual function-preserving cystectomy requires exclusion of high-risk patients. And bladder neck, prostatic urethra, and prostate involvement

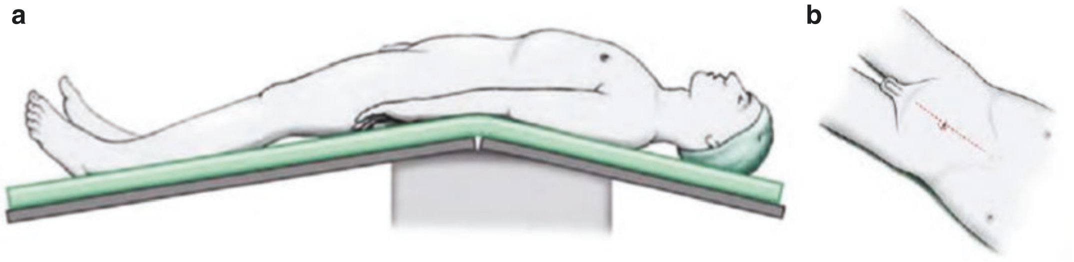

**Fig. 10.10** (**a**) The patient is placed in a hyperextended supine position, and (**b**) long midline incision, a large incision is made in the middle of the abdomen from just above the umbilicus

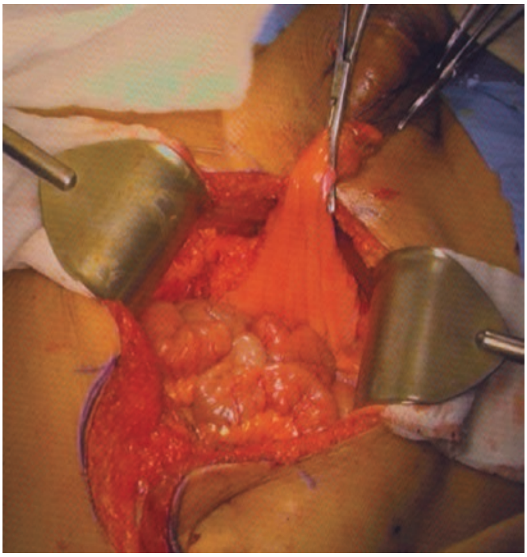

**Fig. 10.11** Mobilization and division of the umbilicus

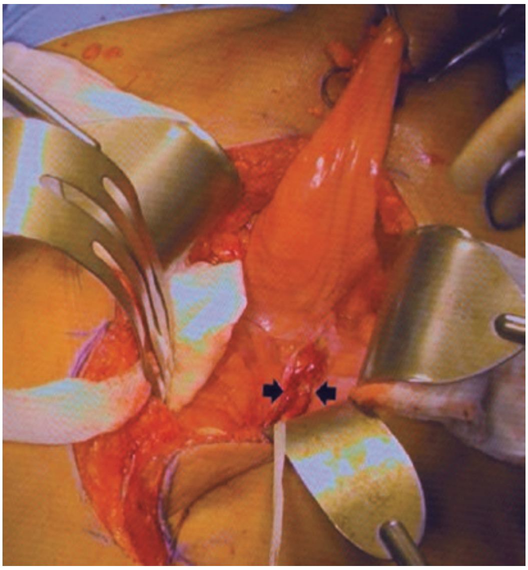

**Fig. 10.12** Right ureter (arrow) dissection

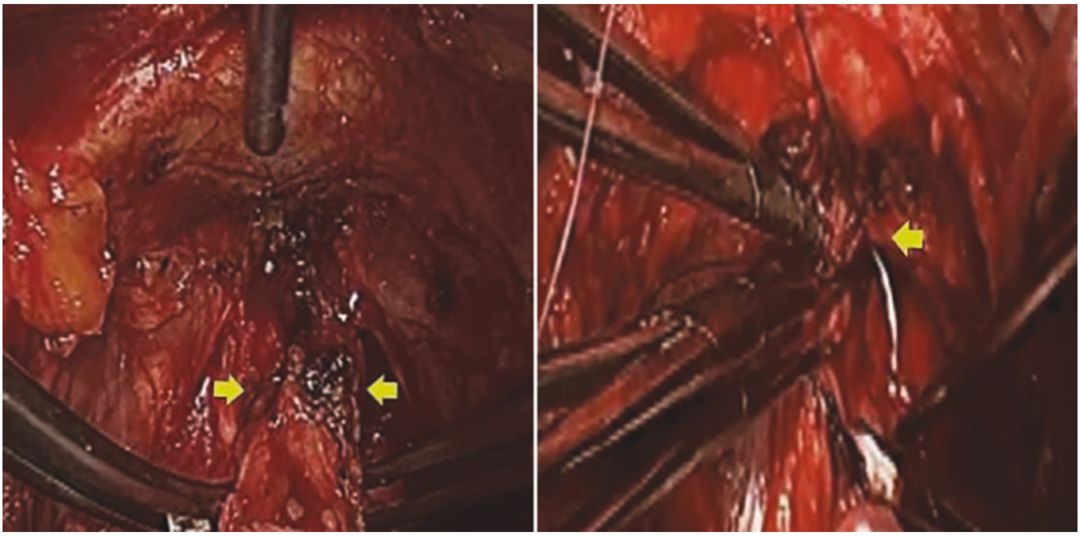

**Fig. 10.13** Dorsal venous complex (arrow) is taken with Allison clamp and DVC ligation is performed

patients [102, 103]. However, there is no clear basis for multifocal tumors and CIS [104].

Sexual function-preserving cystectomy should be performed in patients with low clinical stage and long-life expectancy. And there should be no accompanying prostate cancer and proper sexual function before surgery. There is no age limit, but young men are generally candidates who want to preserve sexual function [104].

Various techniques for sexual function-preserving cystectomy have been reported, depending on the type of neobladder and the method of prostate resection. Terrone et al. introduced the sexual function-preserving cystectomy technique in 1984. The preservation of the neurovascular bundles, seminal vesicles, vas deferens, and ejaculatory ducts and prostatic adenoma enucleation were performed after anterior prostatic capsule incision. The neobladder was anastomosed to the prostatic capsule [105].

Spitz et al. preserved sympathetic nerves and anastomosed the neobladder with the prostatic stoma without removing the prostatic adenoma. The neurovascular bundles, seminal vesicles, vas deferens, and ejaculatory duct were intact [106]. Such sexual function-preserving cystectomy has the advantage of immediate postoperative erectile function and continence and preserving fertility and antegrade ejaculation with acceptable cancer control.

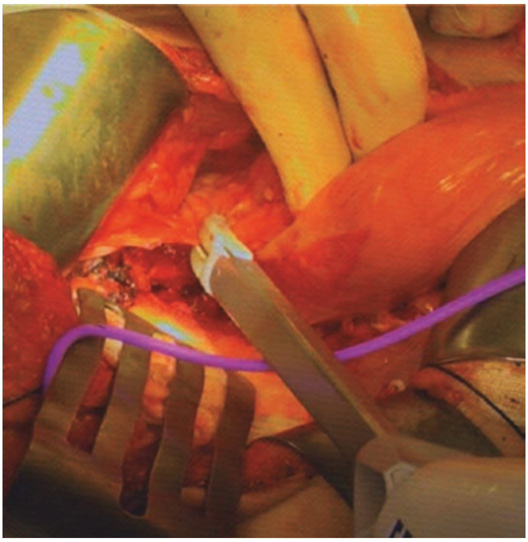

**Fig. 10.14** Left lateral pedicle of bladder is ligated by GIA

#### 10.5.6.3 Ureteral Stent Indwelling

Insertion of a ureteral stent during radical cystectomy increases the upper tract drainage. In addition, it reduces postoperative ileus and metabolic acidosis [82]. However, it is controversial for proper timing of stent removal after RC [83].

#### 10.5.6.4 Frozen Section Analysis of Ureteral Margins

In studies comparing frozen and permanent analysis of the same tissue, the sensitivity of frozen section analysis was 45–80%, and the specificity was 95–99% [107]. Although they have high specificity, low false-positive rate cannot reliably exclude diseased ureters. Sequential removal of the ureteral abnormalities through frozen section analysis is aimed at reducing the risk of recurrence of uretero-enteric anastomosis [107]. However, even if sequential incision is performed following an abnormal frozen section analysis, recurrence of the uretero-enteric anastomosis site is unlikely to occur [108]. Patients

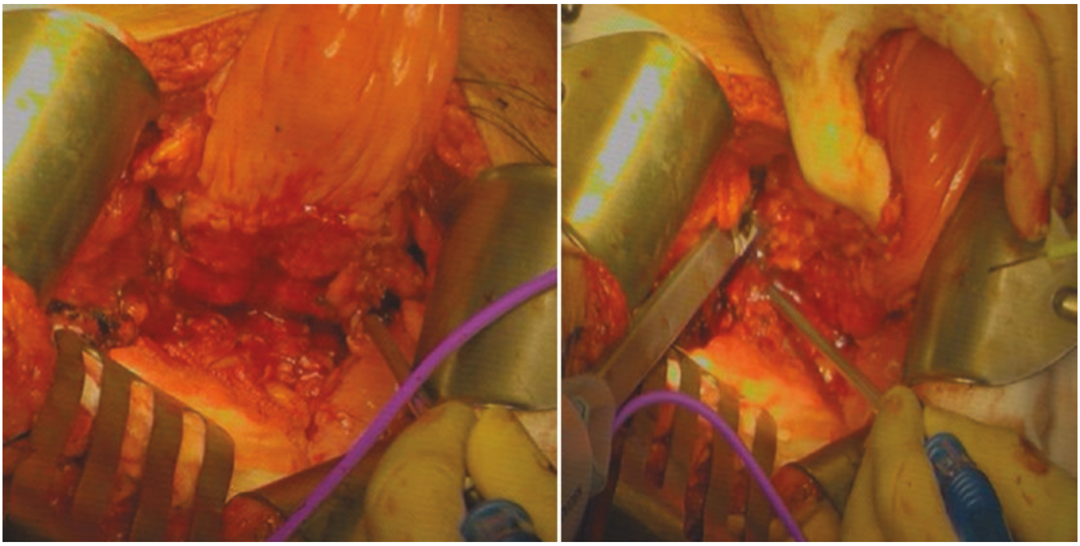

**Fig. 10.15** Douglas pouch exposure and posterior pedicle of bladder is ligated by GIA

with initial positive ureteral margin converted to negative margins had a lower risk of recurrence than those who did not ($p = 0.04$) [109]. Although it is evidence for the usefulness of frozen section analysis, there are limitations as a retrospective study.

Although the CIS remains after sequential resection through frozen section analysis, anastomosis may be performed for short ureter length or for tension-free anastomosis. Several studies have reported that, despite the presence of CIS in the ureter margin, ureteral anastomosis does not cause serious complications or recurrence, and this approach has become the standard of care in a variety of institutions [109–114].

### 10.5.7 Open Radical Cystectomy: Female

In women, radical cystectomy has a different surgical procedure for men. The classic way is to remove the uterus and associated organs together including the bladder, fallopian tubes, ovaries, and vagina. Recently, surgical procedures for preserving gynecologic organs have emerged during radical cystectomy and neobladder formation (Fig. 10.16).

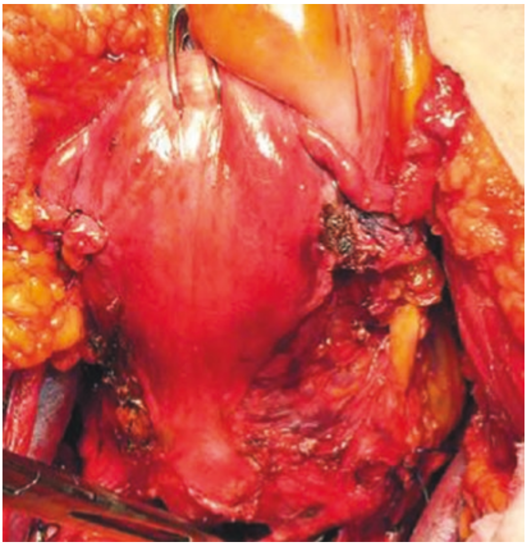

**Fig. 10.16** Vaginal cuff posterior dissection

1. Incision of the posterior vaginal cuff
2. Posterior vaginal wall and defect repair with flap made from the posterior vaginal wall (Fig. 10.17)
3. Circumferential division of the vaginal cuff from the attachments to the cervix (Fig. 10.18)

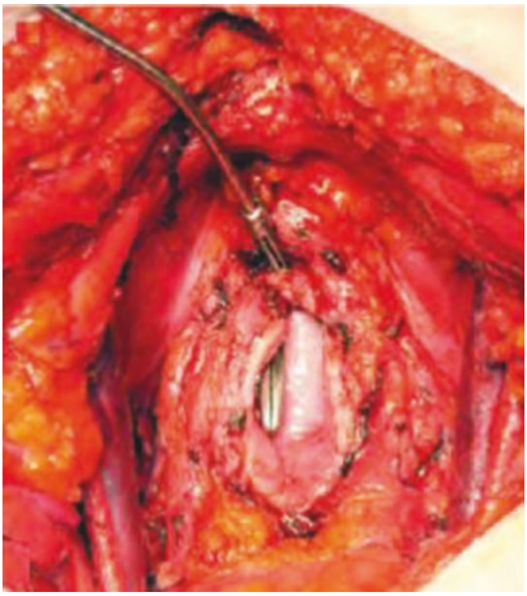

**Fig. 10.17** Defect of posterior vaginal wall

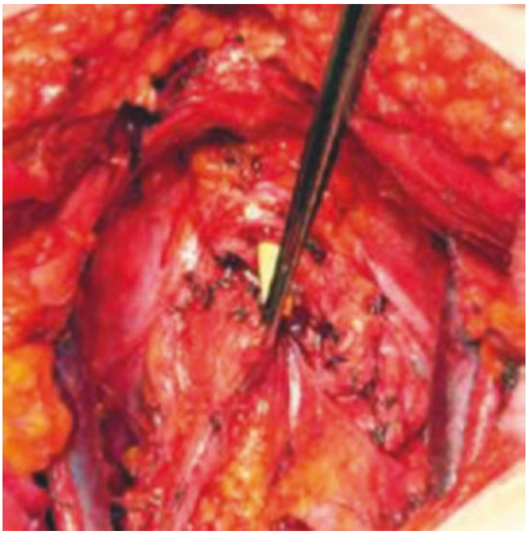

**Fig. 10.18** Closure of the vaginal cuff

## 10.5.8 Robot-Assisted Radical Cystectomy

### 10.5.8.1 Position

Port placement and positioning are very important for successful robot surgery. Safe and highly effective port placement and positioning are needed. And complications such as peripheral nerve paralysis can be prevented by adding a protective pad to the arm and shoulder. A foam pad should be used to cushion all pressure areas, and a shoulder pad and chest tape should be attached to prevent slipping due to the Trendelenburg position. However, the chest tape should be attached to a degree that allows breathing. It is recommended to use progressive compression stockings and occasional compression to prevent thrombosis during surgery (Fig. 10.19).

- The patient takes a dorsal lithotomy Trendelenburg position about 20–25°.
- Padding the shoulders to keep Trendelenburg position.
- Attach both arms to the sides to prevent peripheral neuropraxia.
- Bands on the chest area to keep Trendelenburg position.
- The guard is installed for intubation and face protection.

### 10.5.8.2 Trocar Placement

- The camera port should be located 4 cm above the umbilicus.
- First~second robot trocar: Place the 8 mm robot trocar at a distance of 6–8 cm to the left and right with respect to the umbilicus.
- Third robot trocar and 12 mm working trocar: Place it laterally 8 cm from the first robot trocar and two fingerbreadths apart from the anterior superior iliac spine.
- Additional 12 mm assistant trocar: Lace it in the middle of the camera trocar and the first robot trocar, and place it 6–8 cm away from the two trocars (Fig. 10.20).

### 10.5.8.3 Identification and Transection of the Ureter

When opening the posterior peritoneum above the external iliac artery, the ureter is most easily found. The ureter is mobilized by traction and dissection. Dissection is performed down to ureteral hiatus level and up to common iliac artery upper level.

### 10.5.8.4 Development of the Posterior Plane

The posterior leaflet of Denonvillier's fascia is examined and dissected up to the apex level of the prostate. During this process, the posterior pedicle is also developed (Fig. 10.21).

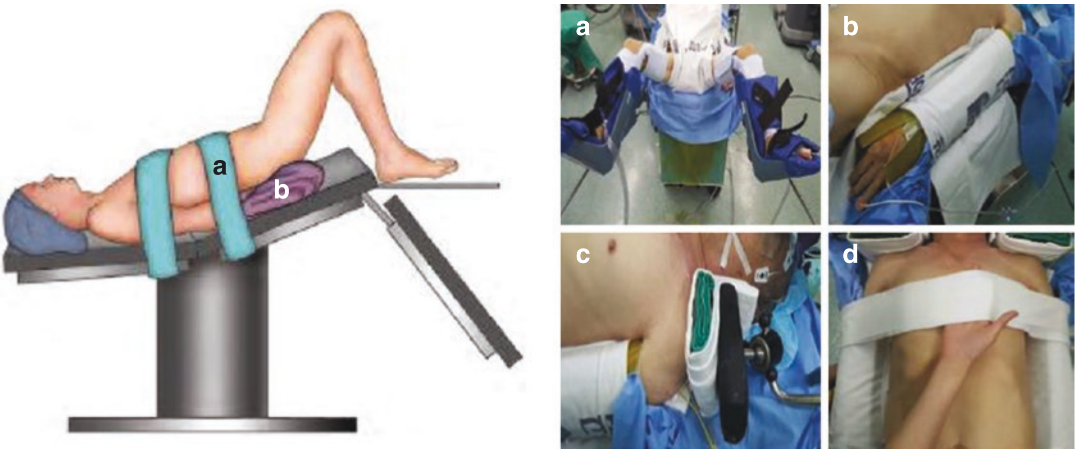

**Fig. 10.19** Patient positioning, (**a**) hip and knee flexion, (**b**) arm positioning, (**c**) shoulder pad positioning, (**d**) chest band positioning

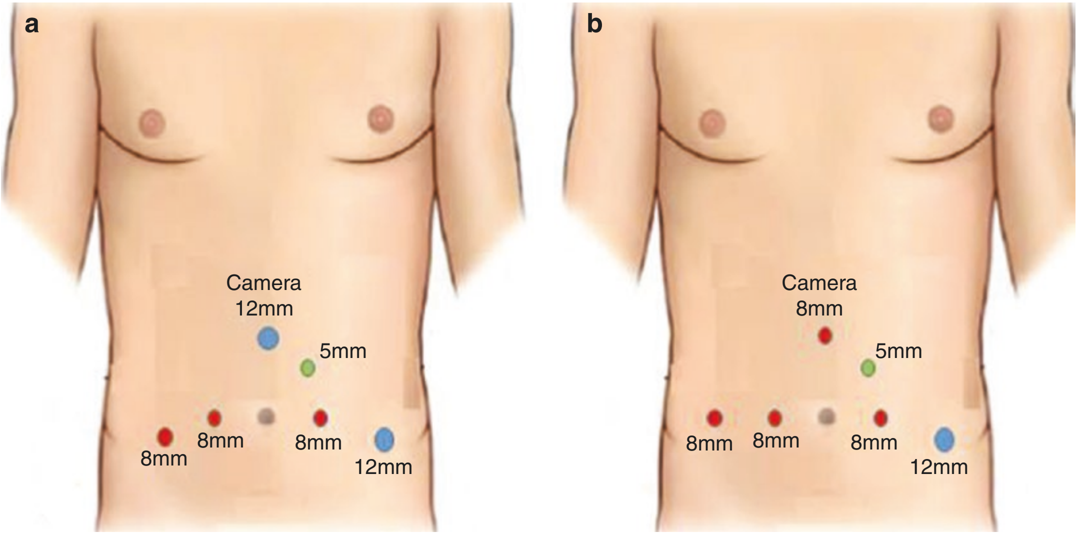

**Fig. 10.20** Port placement. The robotic arm ports are placed on the same level as that of the camera port if extended PLND is to be performed: (**a**) da Vinci Si, (**b**) da Vinci Xi

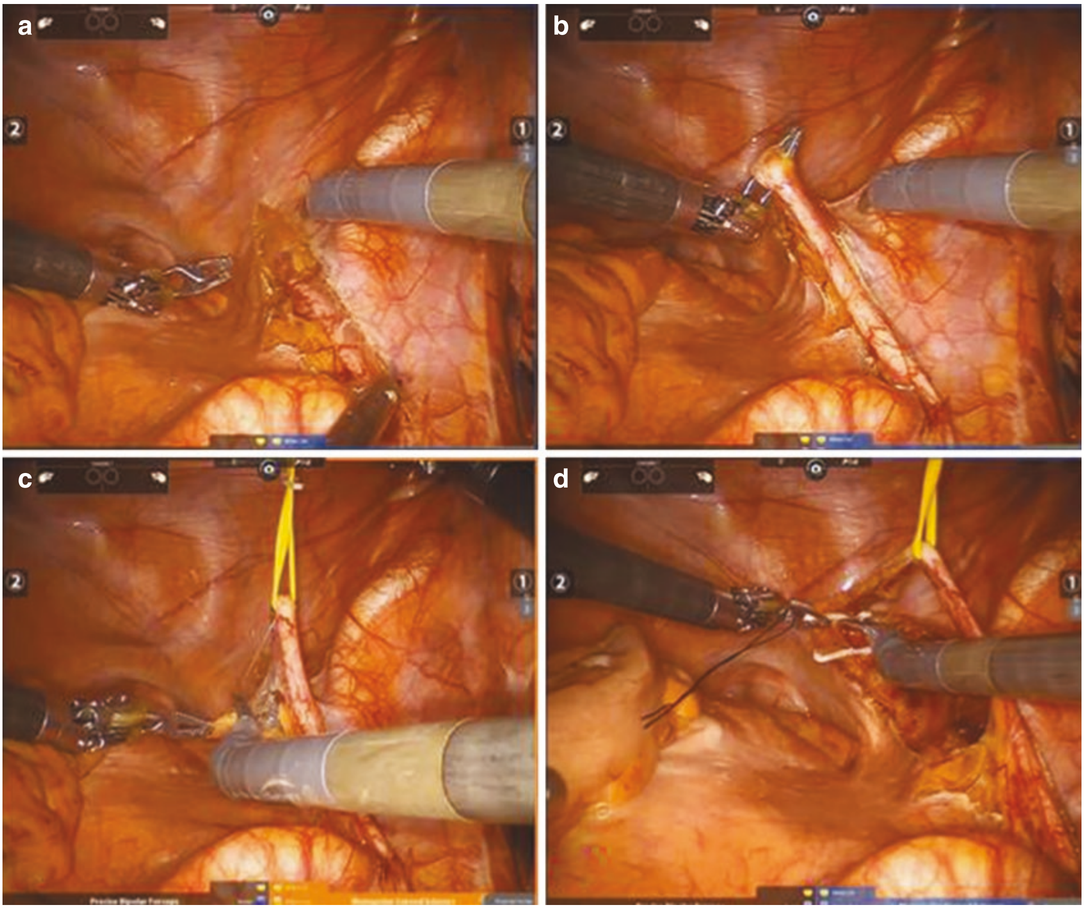

**Fig. 10.21** Ureteral mobilization. (**a**) Posterior peritoneum overlying the external iliac artery is opened lateral to the right colon. (**b**, **c**) Identification of the ureter. (**d**) Ureter being clipped at bladder insertion

#### 10.5.8.5 Separation of Posterior Pedicle

Divide bilateral posterior pedicles. If nerve-sparing technique is performed, avoid using electrocautery and energy devices near the neurovascular bundle (Fig. 10.22).

#### 10.5.8.6 Separation of Anterior Pedicle

The anterior pedicle is the area between the pelvic side wall and the lateral side of the bladder, including the vas deferens, superior vesical artery, and the umbilical artery. If nerve-sparing technique is performed, avoid using electrocautery and energy devices near the neurovascular bundle (Fig. 10.23).

#### 10.5.8.7 Dropping of the Bladder

When the posterior and lateral pedicles of the bladder are separated, only the anterior portion of the bladder is attached to the abdominal wall.

Develope a space between the abdominal wall and the bladder by incising bilateral medial umbilical ligaments.

Dissect the Retzius space and open the endopelvic fascia (Fig. 10.24).

#### 10.5.8.8 Ligation and Division of Dorsal Vein Complex (DVC) and Urethral Resection

In coagulation and incision of DVC using bipolar electrocautery and monopolar electrocautery, up

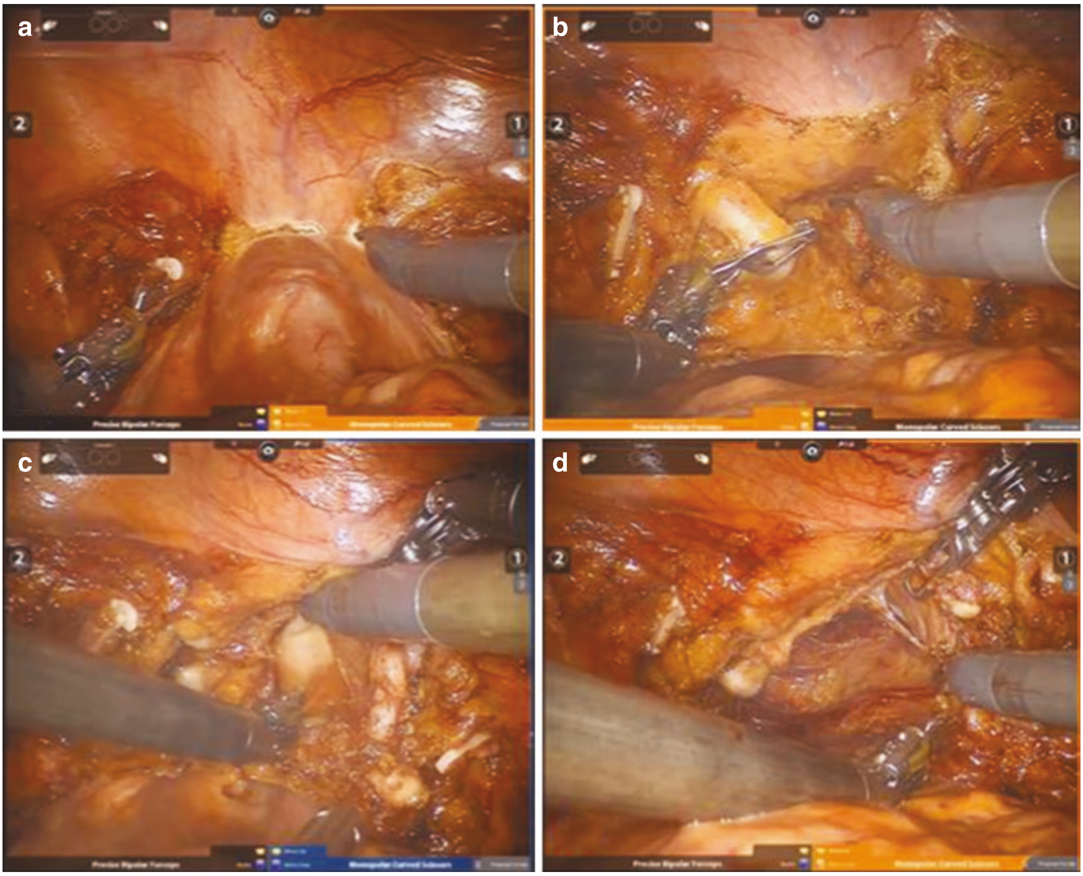

**Fig. 10.22** (**a**) Visualization of the posterior peritoneum to be incised. (**b**–**d**) Posterior dissection to reveal the vas deferens, seminal vesicles, and Denonvillier's fascia

and down continuous suture is performed using V-loc on the cutting section of the DVC. When using the nerve-sparing technique, cut the DVC with scissors and continuously suture the DVC in the same way. After DVC ligation, cut out the urethra exposed under the DVC (Fig. 10.25).

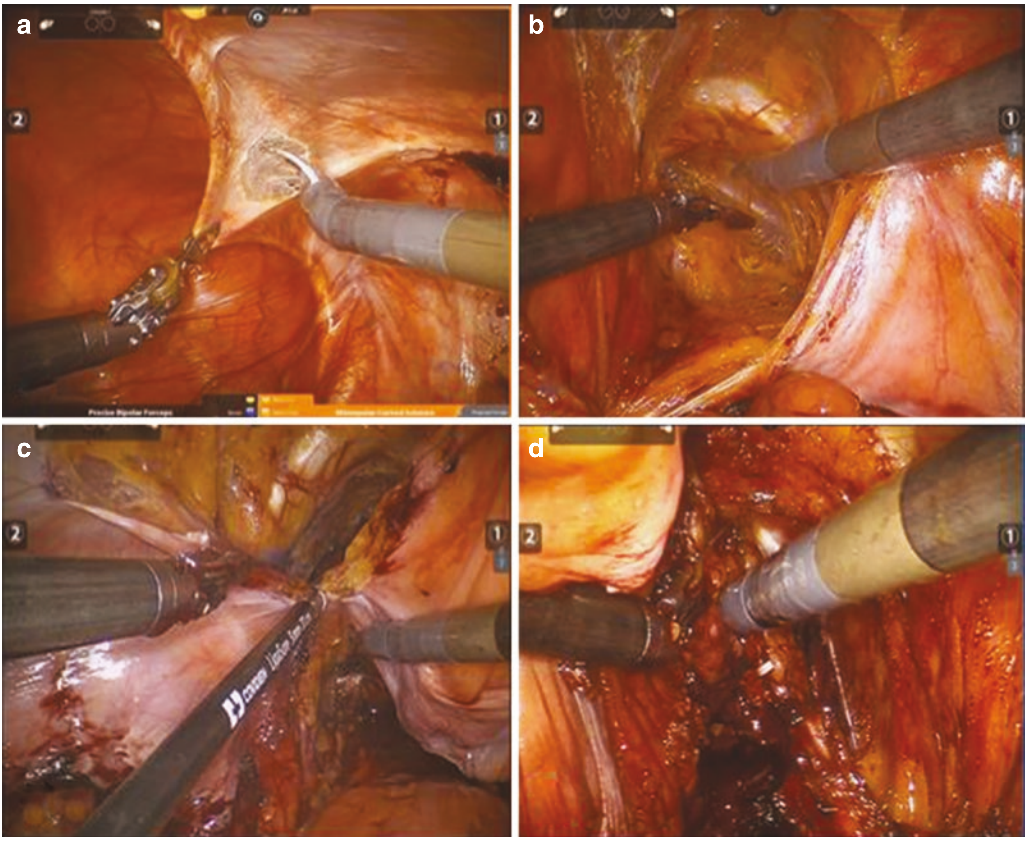

**Fig. 10.23** (**a**, **b**) Development of the anterior pedicle, shown on the patient's right side. (**c**) Anterior pedicles are controlled using energy devices. (**d**) Vesical and prostatic pedicles are controlled using Hem-o-Lok clips or a stapler

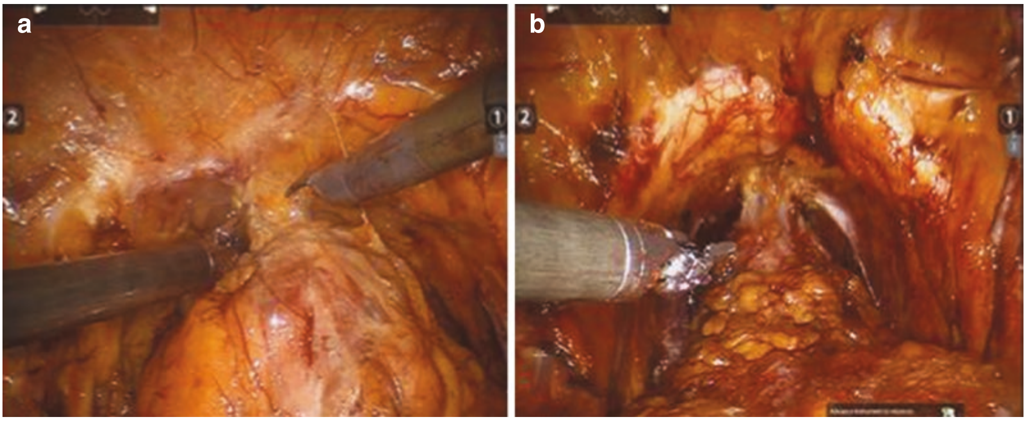

**Fig. 10.24** (**a**) Dropped bladder. (**b**) The space of Retzius is completely dissected. (**c–d**) Suture ligation with 2-0 Vicryl on a CT-1 needle passed underneath the DVC

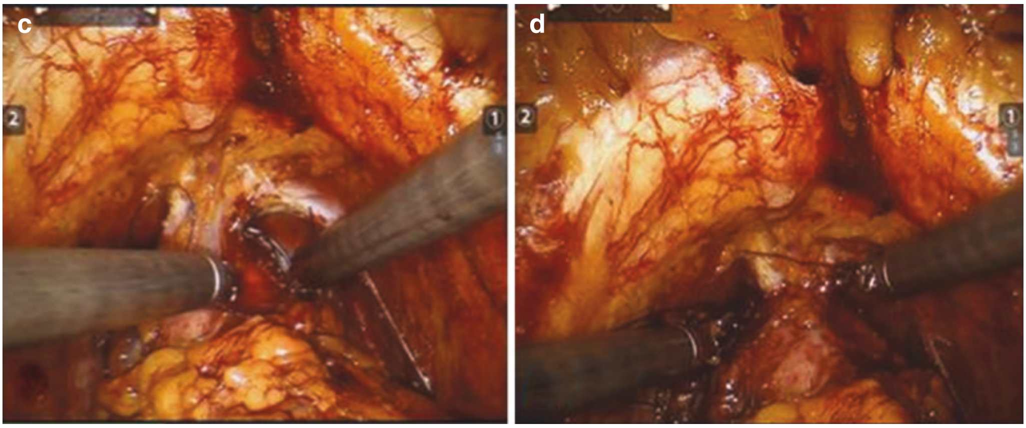

**Fig. 10.24** (continued)

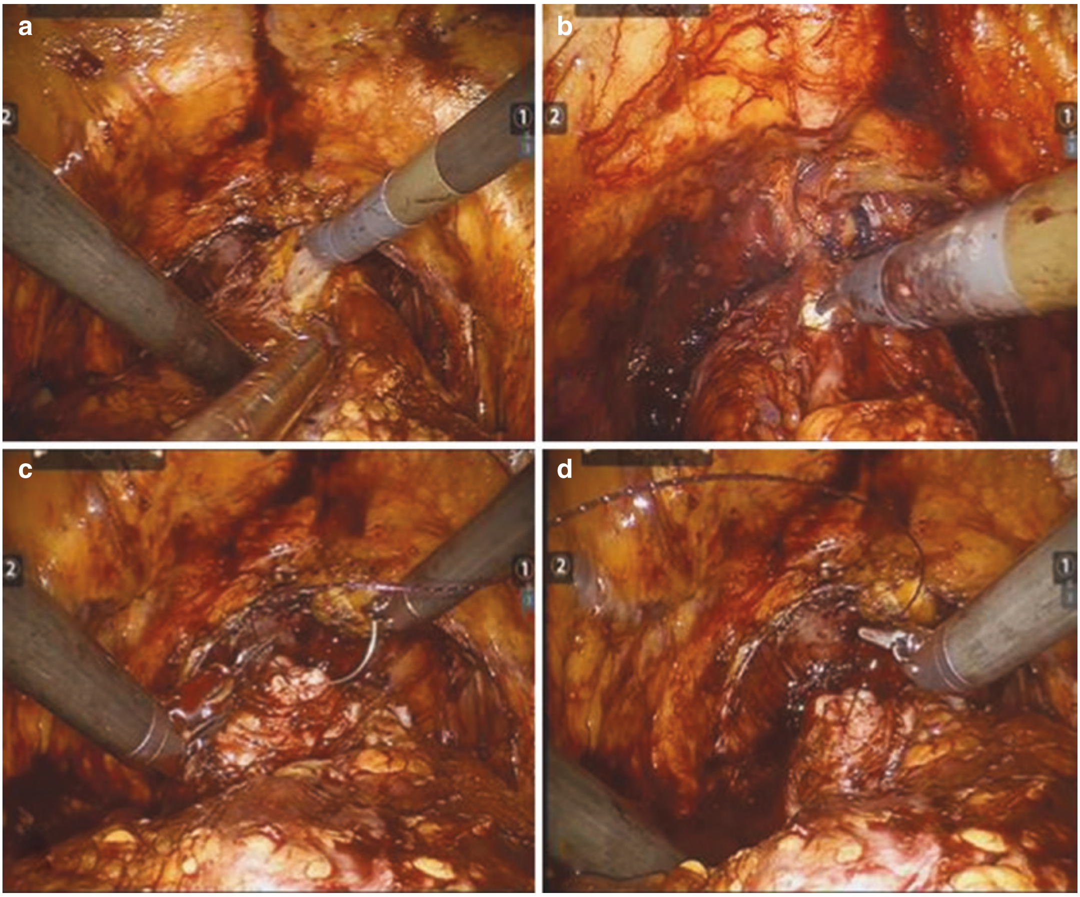

**Fig. 10.25** (**a**, **b**) Urethral resection. (**c**, **d**) Suture the cut urethra to prevent leakage of urine from the bladder

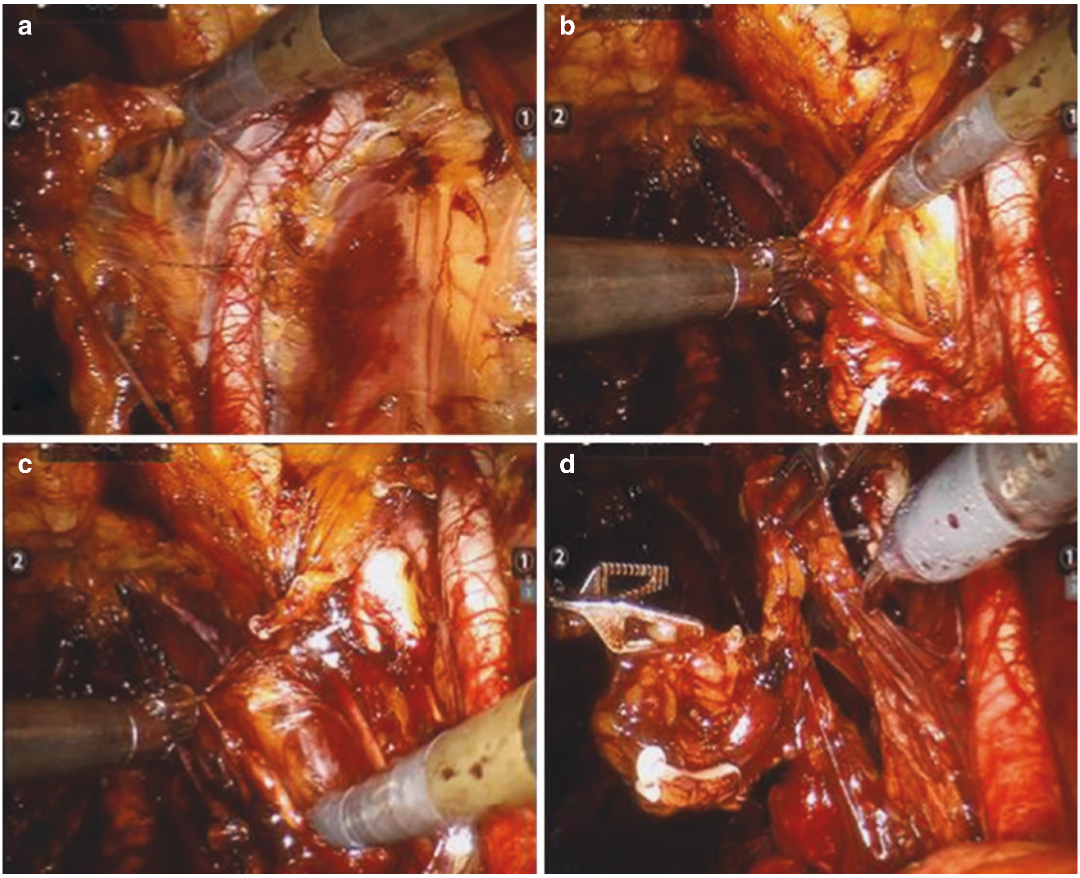

**Fig. 10.26** (**a**–**d**) Pelvic lymph node dissection. The procedure is described in the enclosed video files (https://www.youtube.com/watch?v=XOLUx3A5NFU and https://youtu.be/gUUwwZckSUc)

#### 10.5.8.9 Extended Pelvic Lymph Node Dissection

Extended pelvic lymphadenectomy is a component of accurate staging and also affects the oncologic outcome.

The range of extended pelvic lymph node dissection includes the bilateral external iliac, internal iliac, obturator, common iliac, and inferior mesenteric artery. And preparacaval, preparaaortic, and lymph nodes around presacral (Fig. 10.26).

## 10.6 Urinary Diversion

### 10.6.1 Preoperative Preparation

#### 10.6.1.1 Preoperative Imaging

Preoperative imaging studies provide information about the upper urinary system, including anatomical variations. It also provides information on the surgical intervention and the presence of inflammatory disease in the intestines used for urinary diversion.

#### 10.6.1.2 Preoperative Laboratory Testing

Functional evaluation of renal function: Renal function decreases after urinary diversion in about 70% of patients. Patients with an estimated glomerular filtration rate >40 mL/min may be subject to continent diversion. On the other hand, incontinent diversion is recommended for patients with lesser functions [115].

Functional evaluation of hepatic function: In patients undergoing continent urinary diversion, the risk of hyperammonemic encephalopathy may be increased by increasing ammonium chloride absorption as a diversion luminal surface [116].

#### 10.6.1.3 Considering Comorbidities

Preoperative comorbidities affect clinical outcomes such as postoperative morbidity and mortality [117]. The EAU guideline recommends verifying preoperative comorbidity through validation methods such as the Charlson Comorbidity Index [20]. In addition to complications, age also affects postoperative clinical outcome. More than three complications or more than 70 years are associated with increased mortality [118]. This suggests that preoperative geriatric assessment is also needed. Although urinary diversion indication does not establish specific criteria for complications, ileal conduit is recommended for older patients and those with multiple complications.

#### 10.6.1.4 Preoperative Bowel Preparation

Urinary diversion requires bowel preparation before surgery. When urinary diversion is performed, a detubulization step is required. During detubulization, the bowel is opened, and the fecal material inside the bowel is exposed to the abdominal cavity, which is the surgical field. For this reason, preoperative bowel preparation is necessary [119].

### 10.6.2 Segments to Urinary Diversion

Urinary diversion can use various parts of small and large bowel. Ileum is the most used. In addition, the stomach, jejunum, and colon are used. Urinary diversion using the jejunum and stomach is not recommended due to metabolic consequences after use. The distal ileum or cecum along with the ascending or sigmoid colon is commonly used because it has the least effect of metabolism [120] (Fig. 10.27).

**Stomach** Available sites in stomach are antrum pylori or wedge of the fundus where gastroepiploic vessels supply (Fig. 10.27).

**Small Bowel** When urinary diversion is performed with the jejunum, metabolism abnormalities are the most severe. Therefore, the use of jejunum is limited. On the other hand, the ileum is the most commonly used, showing the least metabolic abnormalities. In addition, the jejunum has a single arterial arcade, while the ileum has multiple arterial arcades [121] (Fig. 10.28).

**Colon** Three parts are available (transverse colon, sigmoid colon, cecum). It has a larger diameter than the ileum, can move easily into the

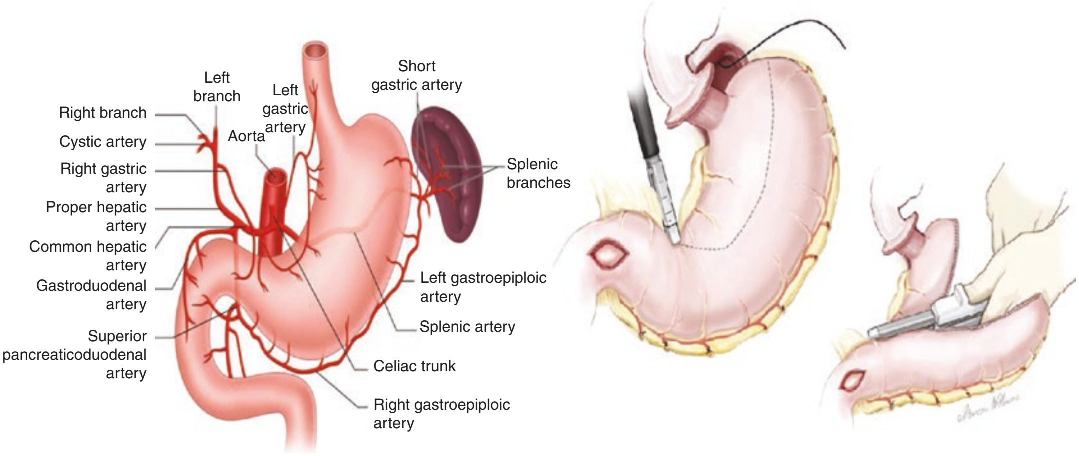

**Fig. 10.27** Stomach segment used for urinary diversion

pelvis, and has less nutritional absorption problems. In addition, bowel obstruction is 4%, <10% of the ileum. However, nighttime voiding is frequent, and there is a serious disadvantage of diarrhea [122] (Fig. 10.29; Table 10.9).

### 10.6.3 Incontinent Diversion (Conduit)

Incontinent diversion does not have internal storage. The urine is not drained after storage but is directly drained from the upper urinary tract directly to the external urostomy appliance. A typical form of incontinent diversion is the conduit [127] (Table 10.10).

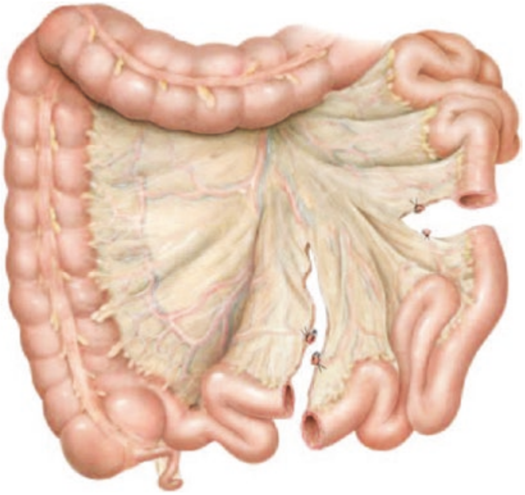

**Fig. 10.28** Small bowel segment used for urinary diversion

#### 10.6.3.1 Selection of Ileal Segment and Its Mesentery

The conduit is the simplest form of urinary diversion using mainly distal ileum. When harvesting distal ileum, approximately 15 cm away from the proximal of the ileocecal valve, 15–20 cm ileum

**Table 10.9** Primary indications and metabolic consequences for use of bowel segments [121–126]

| Bowel segment | Metabolic consequences | Clinical symptoms |
|---|---|---|
| Gastric | Metabolic alkalosis (PH↑, K↓, Cl↓, hypergastrinemia) | Hematuria-dysuria syndrome<br>Dehydration, lethargy, seizures, respiratory distress |
| Jejunum | Metabolic acidosis (PH↓, Na↓, Cl↓, K↑, azotemia) | Dehydration, nausea/vomiting, weakness, lethargy, seizures |
| Ileum | Metabolic acidosis (PH↓, Cl↓, K↑, HCO3-↓, azotemia) | Fatigue, anorexia, weight loss, diarrhea, polydipsia<br>$B_{12}$ and fat-soluble vitamin deficiency<br>Diarrhea, urinary calculi, cholelithiasis |
| Colon | Metabolic acidosis (PH↓, Cl↓, K↑, HCO3-↓, azotemia) | Fatigue, anorexia, wt. loss, diarrhea, polydipsia<br>Pyelonephritis<br>Adenocarcinoma at anastomotic site |

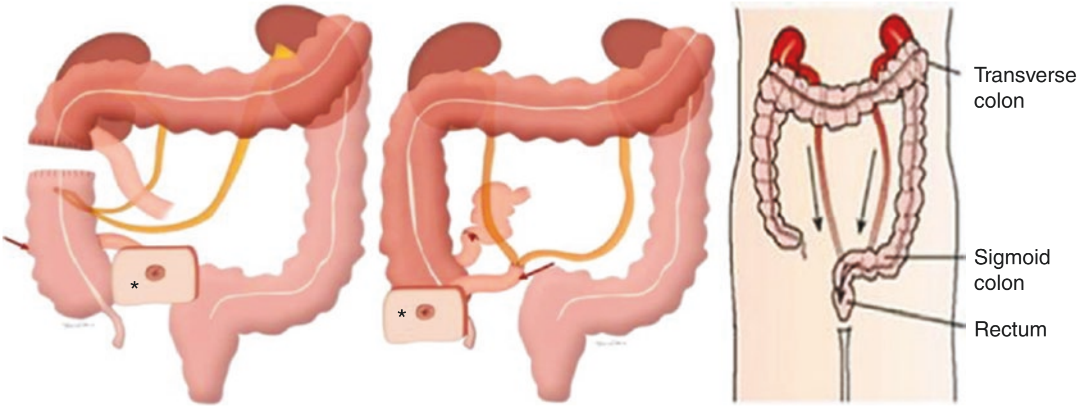

**Fig. 10.29** Colon segment used for urinary diversion (Table 10.9)

**Table 10.10** Considerations of incontinent diversion

| Indications | Advantage | Disadvantage |
|---|---|---|
| Old age<br>Multiple comorbidities<br>Contraindication of intestinal surgery | Short operation time<br>Few perioperative complication<br>Little malabsorption<br>Cut a short length of bowel | Complications related to stoma (stoma stenosis, skin irritation)<br>Relatively high risk of reflux |

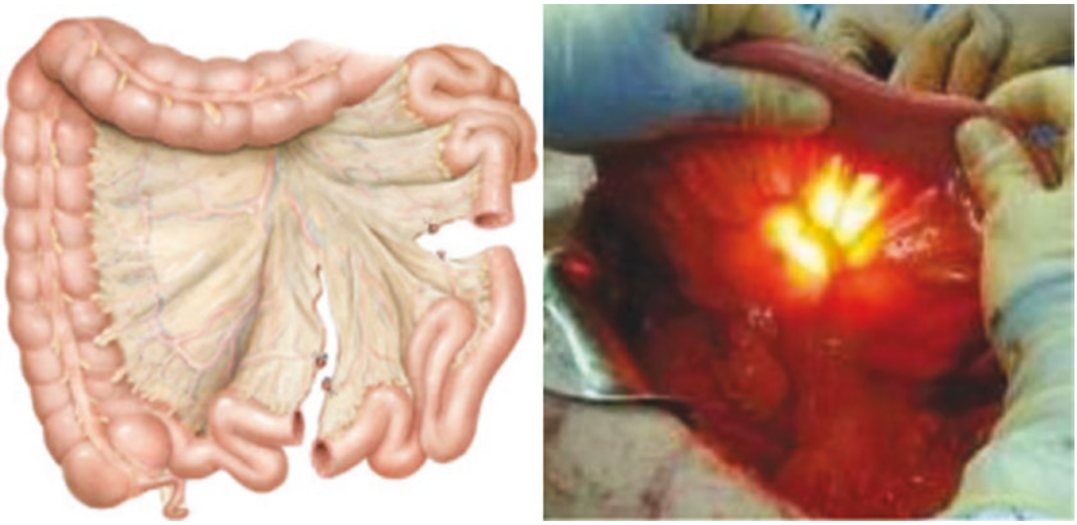

**Fig. 10.30** Division of mesentery

is used. Three factors must be considered when determining the length of ileal segment:

- Consider whether the length of the ureters is anastomosis without tension. Especially the Lt ureter.
- Consider the distance to the abdominal skin and the thickness of the fat and muscle.
- Consider the size of the stoma to be created.

#### 10.6.3.2 Division of Mesentery

Light is projected on to ileal mesentery to confirm major mesenteric artery arcade (Fig. 10.30).

At the mesentery division, select the feeding vessels at both ends from the mesentery vessel loop to the bowel vessel loop so that the mesentery vascular supply is maintained, and cut along both sides of the vessel.

The length of the mesentery should be sufficiently flexible to allow fixation of the ileum distal end to the fascia and skin without tension.

At the mesentery division, the distal end should be cut longer than the proximal end.

#### 10.6.3.3 Bowel Resection and Reanastomosis

In the case of bowel division, the GIA 60 stapler may be used or the clamp may be used in a traditional manner. After bowel resection, the bowel is divided into two sections, one to be used for conduit and the other for reanastomosis. The part to be the conduit is located behind the part to be reanastomosed. Bowel reanastomosis is mostly side-to-side anastomosis, using the GIA 60 stapler. When inserting the GIA stapler into the bowel, make sure that the bowel mesentery faces outward from the GIA stapler. After reanastomosis, the luminal patency must be confirmed by touching with the hand (Fig. 10.31).

#### 10.6.3.4 Stitch of Proximal End of Conduit

The proximal end of the bowel segment to be a conduit is closed by suture without using a GIA

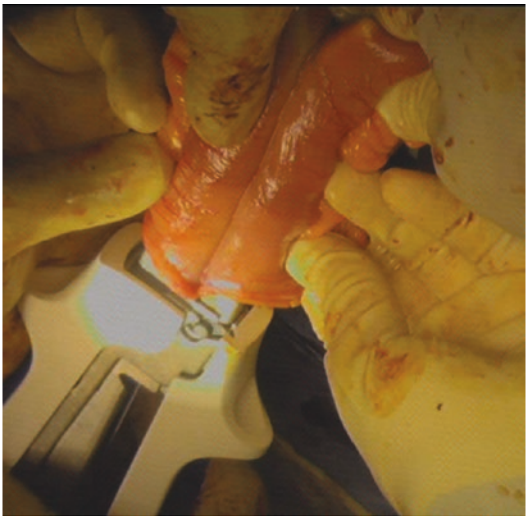

**Fig. 10.31** Bowel anastomosis with GIA

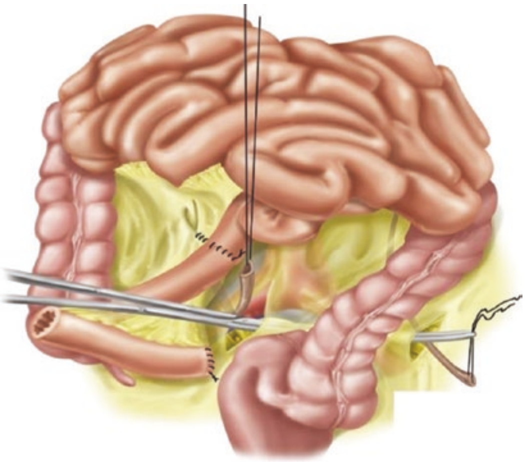

**Fig. 10.32** Ureter pass through the back of the sigmoid mesentery

stapler. If the staple is exposed inside the bowel using GIA stapler, it can cause the formation of stones in the conduit. After the proximal end is closed, the saline is irrigated to the conduit to check for leaks and remove the mucous content inside the conduit.

#### 10.6.3.5 Preparation of Ureter

Generally, if a conduit entrance is made on the right lower abdominal wall, the opposite ureter must pass through the back of the sigmoid mesentery to reach the Rt lower posterior peritoneum. To avoid tension in the ureter, the retrosigmoidal tunnel should be wide enough that it does not damage the sigmoid vascular pedicle. The ureter should be dissected enough to allow anastomosis without tension, and care must be taken to preserve the vascular pedicle running medial the ureter. Traumatic handling of the distal ureter should be avoided (Fig. 10.32).

#### 10.6.3.6 Ureteroileal Anastomosis

Bricker ureterointestinal anastomosis is commonly used. Ureter spatulation is performed by cutting the inside of the distal end of the ureter vertically. End-to-side mucosa-to-mucosa anastomosis is performed with ileum and spatulated ureter using a fine absorbed suture. An additional reinforcement of the anastomosis site is performed by second layer closure of serosa to serosa. The anastomotic site should be located anterior to the ileum. After the anastomosis is complete, fill the conduit with saline and check for leaks in the anastomosis site (Fig. 10.33).

#### 10.6.3.7 Stoma Formation

The proper location of ileal conduit is in the right abdominal quadrant between the umbilicus and anterior superior iliac spine (ASIS). After circular skin incision in the stoma position, rectus fascia is incised in a cross shape. The rectus abdomen is bluntly dissected and the peritoneum is incised. The distal end of the conduit is pulled out of the skin through the already created incision. A 3–4 cm ileal segment is extracted from the skin. Dissect bowel mesentery sufficiently to avoid retractile tension when the ileal segment is pulled out of the skin. Insert your fingers into the distal end of the ileal segment to check that it is not narrowed, tensed, or angled when passing through the skin and muscles. Rectus fascia and stoma base are sutured in 3, 6, 9, 12 direction using 3–0 vicryl to fix the stoma to the rectus fascia. Avoid direct fixation stitches to mesentery. After making the nipple shape, fix the distal end of the stroma circularly in the skin subepithelium (Fig. 10.34).

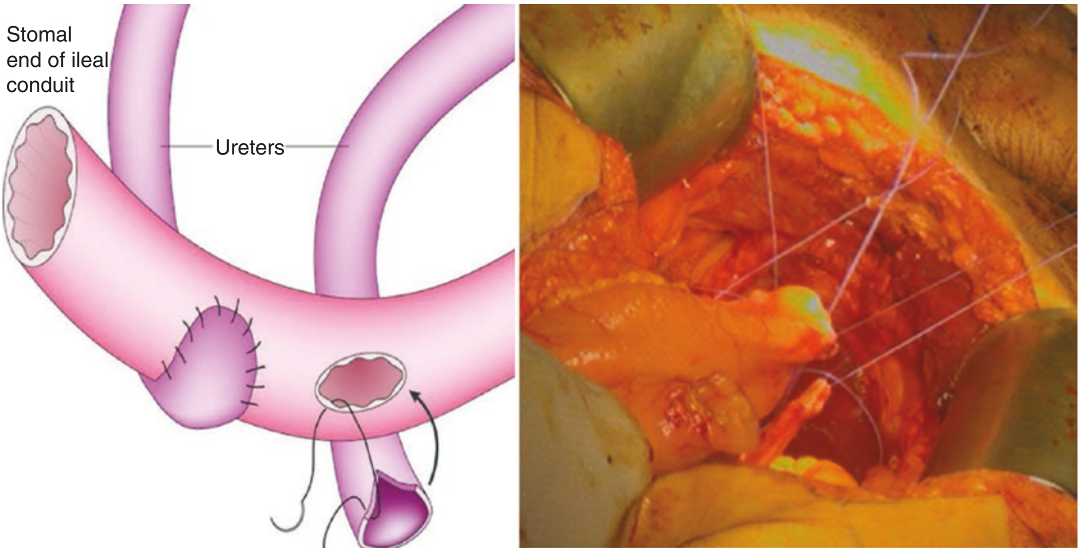

**Fig. 10.33** Ureteroileal anastomosis

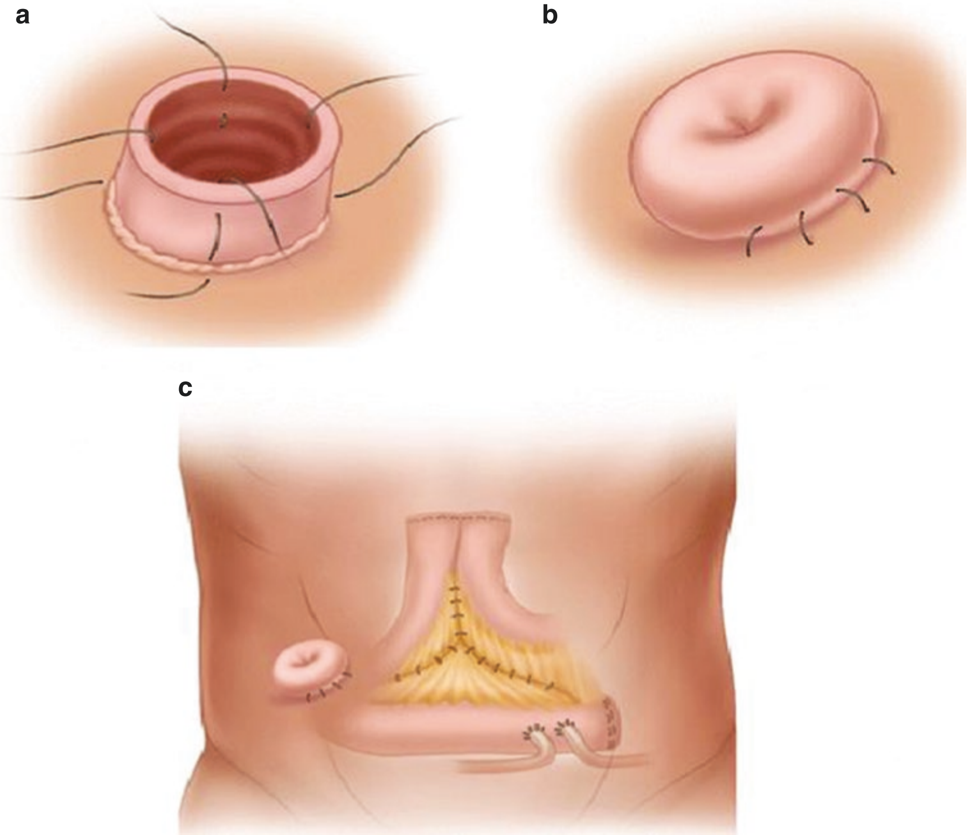

**Fig. 10.34** Stoma formation. (**a**) The distal end of the conduit is pulled out of the skin, (**b**) everted and stitched to the skin surface. (**c**) The stoma should be sited in the right lower quadrant of abdomen

### 10.6.3.8 Continent Diversion (Neobladder)

A representative form of continent diversion is the neobladder. The neobladder is a surgical procedure in which a bowel is cut and then detubulized, and a detubulized bowel is used to create a spherical reservoir and connect it to the urethral stump. Mostly the ileum is mainly used; when harvesting distal ileum, approximately 15 cm away from the proximal of the ileocecal valve, 60–75 cm ileum is used. Mesentery and bowel resection and bowel reanastomosis are performed in the same way as the conduit [128] (Table 10.11).

### 10.6.3.9 Ileal Reservoirs

Detubulized resected ileum. For detubulization, place the mesentery downwards and incision along the opposite upper direction. Detubulized ileum creates a spherical reservoir which should not be done with a stapler or nonabsorbable suture because there is a risk of stone formation. There are many forms of reservoir. Representing two of them are Studer type and Hautmann type (Fig. 10.35).

### 10.6.3.10 Studer Type

Studer type is one of the most common reservoir forms. The advantage of the Studer type is that it can be made of the simplicity of the structure and the length of the short ureter. The reservoir part is made in the shape of a double-folded U and a long tubular segment of the afferent limb in which the ureters meet. Long tubular segments prevent reflux. The reservoir used about 40–44 cm segment of distal ileum, and the afferent limb used about 15 cm [129] (Fig. 10.36).

The anastomosis of the neobladder and urethra makes a 6-circular stitch with 2-0 vicryl. A Foley catheter (18Fr 5 cc balloon) is inserted into the neobladder through the urethra and then ties the anastomotic stitch. A leak test is performed by filling the neobladder with saline through the Foley catheter.

### 10.6.3.11 Hautmann Type (W Type)

The Hautmann type was designed to be closer to the larger capacity, more spherical shape, to optimize the initial volume and reduce nighttime urinary incontinence. The reservoir used 60–70 cm segment of distal ileum. The bowel is detubulized and made into a W-shaped neobladder. Make a neobladder neck with a hole in the lower part of the neobladder. An anastomosis of the neobladder neck and urethral stump is performed [128] (Fig. 10.37).

**Table 10.11** Considerations of continent diversion

| | Advantage | Disadvantage |
|---|---|---|
| *Absolute contraindications* | Similar to normal voiding<br>Preservation of body image | Many perioperative complications<br>Long operation time<br>Long postoperative recovery time<br>Possibility of voiding dysfunction<br>Day and night time incontinence<br>Need for CIC |
| Presence of metastasis | | |
| Tumor at prostatic urethra | | |
| Renal insufficiency | | |
| Hepatic insufficiency | | |
| Physical disability to perform CIC | | |
| *Relatively contraindications* | | |
| Multiple comorbidities | | |
| Prior pelvic radiation | | |
| Inflammatory bowel disease | | |
| Malignant bowel disease | | |
| Abnormal ext. sphincter function | | |
| Urethral stricture and obstruction | | |
| Neurological diseases associated with impaired continence | | |

*CIC* clean intermittent catheterization

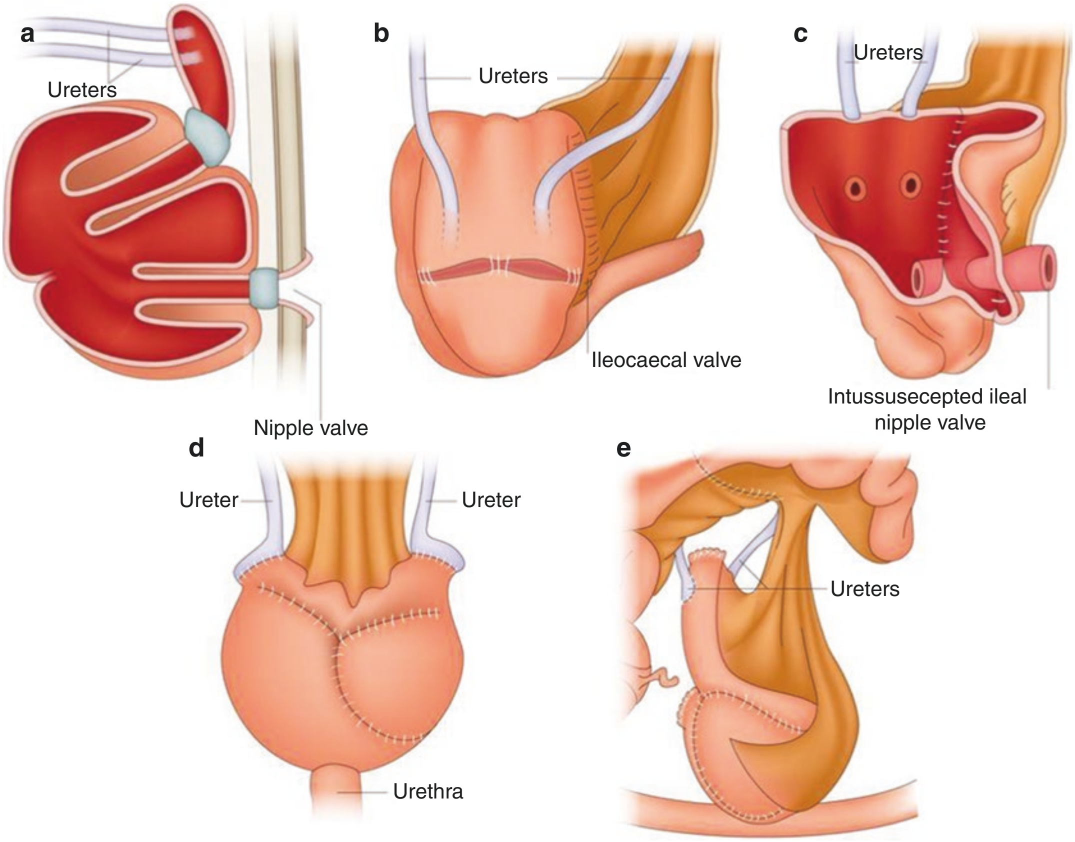

**Fig. 10.35** Types of urinary diversion. (**a**) Kock pouch. This diversion was developed by Kock and consists of an ileal reservoir with an intussuscepted nipple valve. (**b**) Indiana pouch. This diversion consists of an ileocecal reservoir with ileocecal valve. (**c**) Mainz pouch. This diversion consists of an ileal reservoir with an intussuscepted ileal nipple valve. (**d**) Hautmann neobladder. This diversion is an orthotopic neobladder using an ileal segment that is detubularized in a "W" or an "M" shape and anastomosed to the urethra with the ureters tunneled into the reservoir. (**e**) Studer neobladder. This diversion uses ileum that is detubularized into a "U" shape

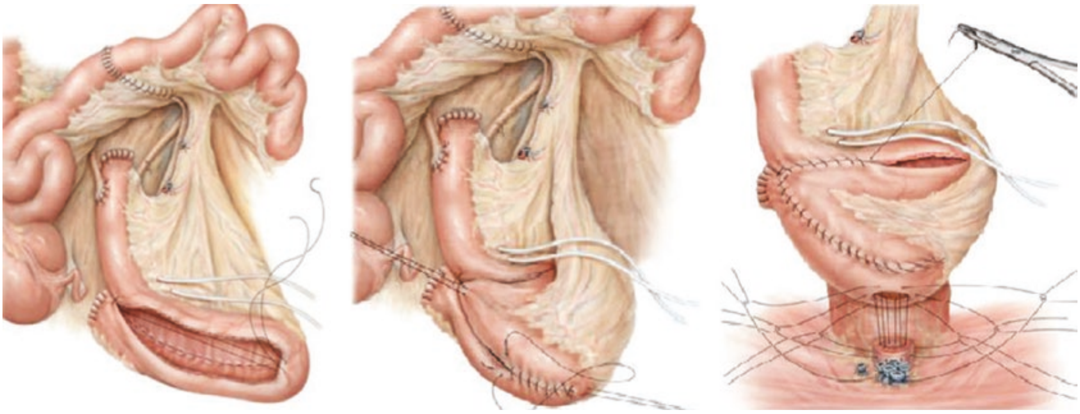

**Fig. 10.36** Studer type neobladder

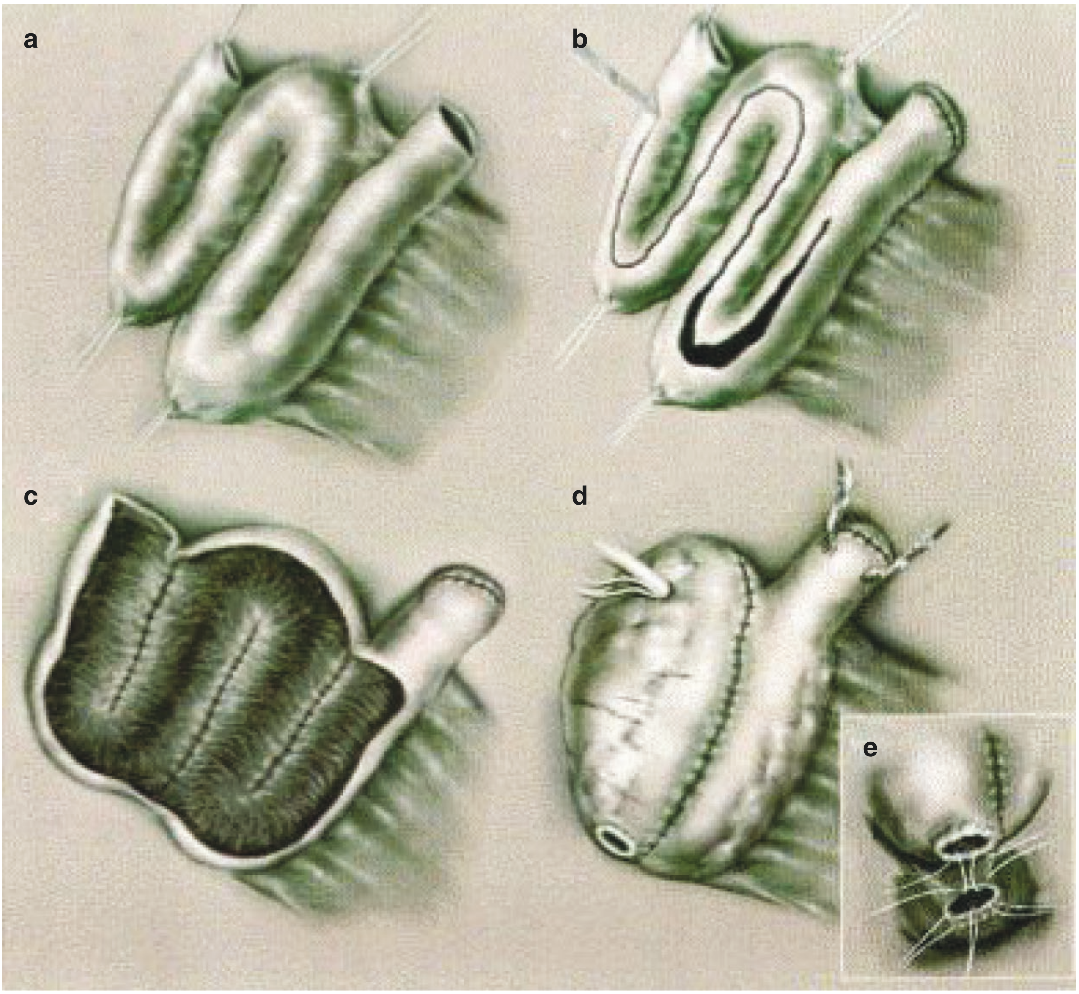

**Fig. 10.37** Hautmann type neobladder. (**a**) Isolated 60-70 cm segment of distal ileum and arranged it in a W-shape. (**b**) Incised along its antimesenteric border (**c**) Sutured the four limbs of W shape close to the sphere. (**d**) Aastomosed to the ureter and urethra

### 10.6.4 Urinary Re-Diversion

#### 10.6.4.1 Conversion from the Hautmann Pouch

In the Hautmann pouch, convert to continence reservoir using the appendix. The appendix anastomosis with neobladder and abdominal wall and create a subserosal tunnel with a meso-appendix window (Fig. 10.38).

#### 10.6.4.2 Studer Pouch

In Studer type, converts to ileal conduit using afferent limb. Interpose the ileum when the afferent limb is short and do not close the abdominal wall (Fig. 10.39).

## 10.7 Partial Cystectomy

Partial cystectomy has several advantages over radical cystectomy: preservation of sexual function, maintenance of voiding function, and relatively few morbidity and complications. However, high recurrence rates of 40–70% and poor oncologic outcomes are disadvantages (Table 10.12).

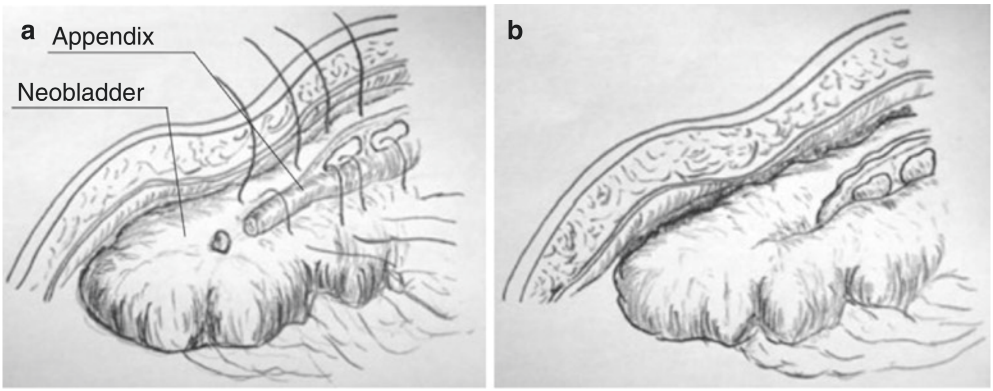

**Fig. 10.38** Conversion from the Hautmann pouch. (**a**) The apex and the proximal side of the appendix is anastomosed to the abdominal wall and neobladder, respectively. (**b**) Windows are created in the mesoappendix, seromuscular sutures are placed through the meso-appendix as a subserosal tunnel

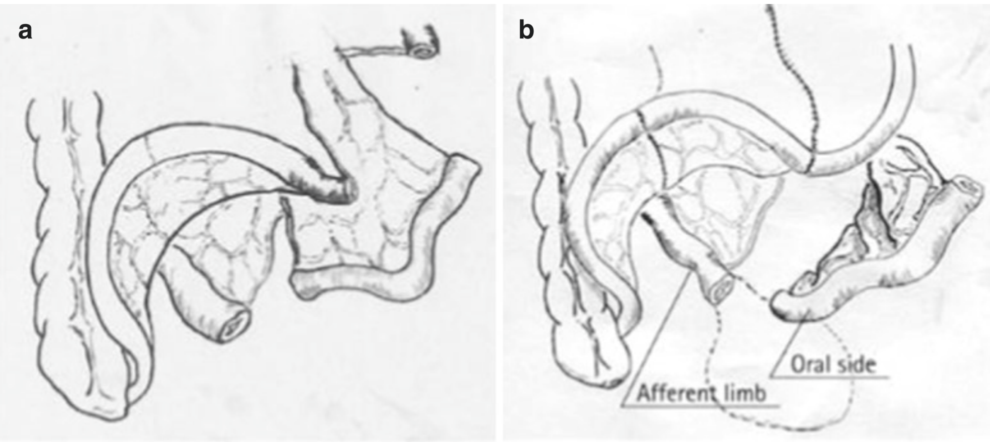

**Fig. 10.39** Conversion from Studer pouch. (**a**) Conversion to an ileal conduit using the afferent limb of the Studer pouch. (**b**) Isolated ileum was interposed between the afferent limb and the left side of the abdominal wall

**Table 10.12** Studies of partial cystectomy

| Study | No. of patients | Stage | Follow-up (months) | Subsequent radical cystectomy (%) | Outcomes |
|---|---|---|---|---|---|
| Holzbeierlein et al. [130] | 58 | cTa–4 | 33.4 | 6.8 | 5-year OS: 69% |
| Kassouf et al. [131] | 37 | cT2–3 | 72.6 | 16.2 | 5-year RFS: 39%<br>5-year CSS: 87%<br>5-year OS: 67% |
| Smaldone et al. [132] | 25 | cT1–2 | 45.3 | 32 | 5-year RFS: 62%<br>5-year CSS: 84%<br>5-year OS: 70% |
| Capitanio et al. [133] | 1573 | pT1–4<br>N1–2<br>M0 | 64 | NR | 5-year CSS: 76.4%<br>5-year OS: 57.2% |
| Fahmy et al. [134] | 714 | NR | 62 | 23.7 | 5-year RFS: 40.3%<br>5-year OS: 49.8% |
| Knoedler et al. [135] | 86 | pT1–4<br>N0–1 | 74 | 19 | 10-year CSS: 58%<br>10-year OS: 36% |
| Golombos et al. [136] | 29 | cT1–2 | 37 | 3.4 | 5-year RFS: 68%<br>5-year OS: 79% |

*OS* overall survival, *CSS* cancer-specific survival, *RFS* recurrence-free survival

## 10.8 Pelvic Lymph Node Dissection

### 10.8.1 The Extent of Pelvic Lymph Node Dissection

Knowledge of the lymph nodes and lymph drainage around the bladder was first established in 1950 by Cooper and Leadbetter [137]. Smith and Whitmore reported that the most common sites associated with lymph node metastasis in bladder cancer are external iliac and obturator lymph nodes [138]. In patients with lymph node metastasis, 74% of patients had positive findings on external iliac lymph nodes, and 65% of patients had node-positive findings on obturator lymph nodes. In addition, 19% of patients with lymph node metastasis showed positive findings on the common iliac node, thus providing the evidence for the standard pelvic lymph node dissection. In another multicenter study, lymph node metastasis around the obturator and iliac vessel lymph nodes was found most commonly, 16% reported that they were found in aortic bifurcation, and 8% reported that they were found in presacral [139, 140] (Fig. 10.40).

In a study based on the SEER database, patients who received LND as bladder cancer had a higher survival rate in 10 years than patients who did not receive LND [141, 142].

There are four categories: limited LND, standard LND, extended LND, and super-extended LND (Table 10.13).

- Limited LND: the obturator lymph nodes
- Standard LND: the obturator, presacral, internal, and external iliac nodes
- Extended LND: the obturator, presacral, internal, external, and common iliac nodes

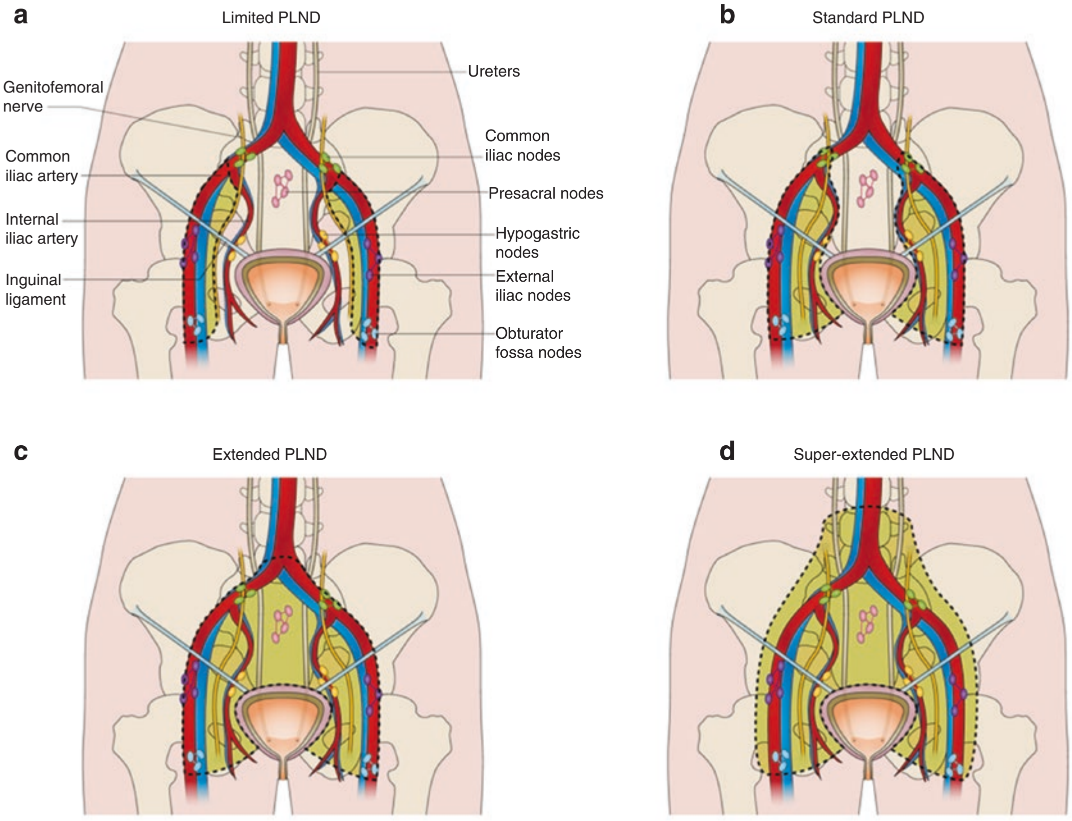

**Fig. 10.40** Anatomical regions of pelvic lymph node dissection

**Table 10.13** Lymph node dissection categories

| | Proximal border | Distal border | Lateral border | Medial border |
|---|---|---|---|---|
| Limited LND | | | External iliac vein | Obturator nerve |
| Standard LND | Bifurcation of common iliac vessels | Circumflex iliac vein | Genitofemoral nerve | Internal iliac vessels |
| Extended LND | Aortic bifurcation | Circumflex iliac vein | Genitofemoral nerve | |
| Super-extended LND | Inferior mesenteric artery | Circumflex iliac vein | Genitofemoral nerve | |

*LND* lymph node dissection

- Super-extended LND: the obturator, presacral, internal, external, common iliac, paracaval, paraaortic, and interaortocaval nodes

### 10.8.2 Standard Versus Extended Lymph Node Dissection

Simone et al. compared the standard LND with the extended LND. The 5-year RFS showed a good prognosis with 42.6% vs 63.1% and 5-year CSS with 50.9% and 68.8%, respectively. Extended LND was an independent prognostic factor for RFS and CSS [143]. In another study comparing LND and extended LND, Dhar et al. reported a 5-year RFS of 67% vs 77% for pT2N0 and 63% vs 71% for pT2N0–2 ($p < 0.001$). Five-year RFS of 23% vs 57% in pT3N0 and 19% vs 49% in pTN0–2 ($p < 0.001$) was reported [144]. In other studies, extended LND is reported to have survival gain compared to standard LND [142].

### 10.8.3 Lymph Node Density and Number

The number of positive LNs is one of the poor prognostic factors.

Several studies have reported that survival outcomes such as OS and DFS decrease with increasing number of positive LNs.

In a retrospective study by the Mayo Clinic, patients with more than four positive lymph nodes had the highest bladder cancer mortality. In another study, prognosis was analyzed using a new three grade nodal classification system with positive LN one, two to five, and five or more. Five-year survival rates were 43%, 22%, and 11%. The more the number of positive LN, the less the survival rate was.

In another study, patients with 2–5 positive nodes had half the survival rate of patients with a single positive node. If there are more than five nodes, the prognosis is not good. However, one of the classification problems based on the number of positive nodes is that the number of positive nodes is affected by the number of nodes that are rescued. The more positive LN, the more positive LN patients.

However, one of the classification problems based on the number of positive nodes is that the number of positive nodes is affected by the number of nodes that are resected. The more resected LN, the more positive LN.

The LN density is the ratio divided by the total number of nodes excluded from the positive LN number [145]. Herr et al. reported that LN density was a stronger predictor of disease-specific survival and local recurrence than TNM staging system [146]. In a meta-analysis of LN density, increased lymph node density was significantly associated with poor prognosis in LN-positive patients. The hazard ratio was 1.45 and 1.45 (95% CI 1.11–1.90) for OS, 1.53 (95% CI 1.23–1.89) for CSS, and (95% CI 1.10–1.91) for RFS [147].

However, there is still debate about the cutoff value of LN density. Stein et al. presented 20% LN density cutoff value. The 5-year survival rate was 43% at 20% or more of LN density value and 8% at <20% ($p < 0.001$, 144]. In a study based on the SEER database, 12.5% of the LN density cutoff values were strong predictors of survival [148]. In addition, the number of LNs removed can affect the LN density. Kassouf et al. reported that LN density acts as a strong prognostic factor with more LN removed [149].

### 10.8.4 Extracapsular Extension of Lymph Node Metastasis

There is little research on the relationship between prognosis and extracapsular extension of LN metastasis. The extracapsular extension of LN metastasis implies extension of the tumor growth out of the LN capsule. This indicates an aggressive tendency of the tumor. Several studies have reported that ECE of LN metastasis is an independent prognostic factor of DFS and DSS in LN-positive bladder cancer and upper urothelial carcinoma [150–152]. Fleischmann et al. reported that ECE of LN metastasis was a strong predictor of RFS and OS ($p = 0.019$) [151]. However, there is also a contradictory opinion. Kassouf et al. reported that ECE of LN metastasis was not a prognostic factor for OS, DSS, and RFS in patients with positive LN [153].

## 10.9 Morbidity and Mortality for Radical Cystectomy

### 10.9.1 Morbidity after Radical Cystectomy

Radical cystectomy involves the bladder, ureter, pelvic lymph node, removal of adjacent organs such as in females the uterus and vagina or in males the prostate and seminal vesicle and urinary diversion using intestines. There is a relatively high risk of complications due to various organs and long operation time. The overall incidence of complications after radical cystectomy is 60%, and the incidence of grade 3 or higher complications is 10% [154, 155]. The blood transfusion rate after RC is about 30% [78]. Considering the immunosuppressive effect of transfusion, there have been many studies on the effect of transfusion on the oncological outcome [78, 79]. Postoperatively, intestinal obstruction is a common complication and has been reported to occur in 23–38% of patients [154, 155]. Early removal of NG tubes and insertion of ureteral stents, chewing gum, the use of appropriate analgesics, and early diastolic function are helpful in reducing these complications [84]. Acute pyelonephritis occurs in 20–25% of patients [154, 155]. In addition, infection due to leakage of uretero-enteric anastomosis site urine may occur. Leaked urine may also be caused by complications such as urinoma. Perioperative ureteral stenting reduces these complications [82]. The incidence of wound-related complications such as hernia and wound dehiscence was reported to be 15–18% [154, 155]. Obesity, elderly, and length of hospital stay are risk factors, and interrupted suture is more effective than wound care for continuous suture [156]. The incidence of symptomatic venous thromboembolism (VTE) after RC is 3–11%. And the incidence varies according to the risk group [67]. For patients receiving RC, thromboprophylaxis using low-molecular-weight heparin injection 12 h before surgery or 6–8 h after surgery or compression stockings or intermittent mechanical air compression stockings are recommended [72, 73]. Extended lymphadenectomy causes complications such as lymphoceles and lymphedema [154, 155]. Nevertheless, extended LND is reported to have survival gain compared to standard LND [142].

### 10.9.2 Mortality After Radical Cystectomy

Mortality after radical cystectomy has been reported to be wide ranging from 1.9 to 9%. This is thought to be due to differences in surgical techniques or patient characteristics [154, 157–159].

In the past, the 30-day mortality rate was frequently used after radical cystectomy. However, due to advances in medical technology, there are more cases in which the 90-day mortality rate is applied recently. Most of the causes of death were myocardial infarction, pulmonary embolism, and sepsis due to infection [155, 158]. The volume of the hospital and the surgeon's experience have been reported to affect mortality after radical cystectomy. In a study using the national cancer database, low-volume hospitals reported a 1.5-fold increase in a 30-day mortality and a 1.2-fold increase in a 90-day mortality compared to high-volume hospitals [160]. Other database-based studies have also reported that high-volume hospitals and surgeons are important factors in mortality after radical cystectomy [161].

### 10.9.3 Prognosis after Radical Cystectomy

There are several factors that can predict prognosis after radical cystectomy. The factors include age, sex, LVI, and histologic variant. Referring to US cancer registry data, the cancer-specific mortality of women is higher than that of men in bladder urothelial carcinoma [162]. One of the reasons for this sex difference is that the diagnosis of the woman is delayed. In women with hematuria, diagnosis of bladder cancer is often delayed due to misinterpretation of symptoms. Sex-specific disparities in hormone receptors have been reported to be due to sex imbalances, but there are also conflicting studies [162].

Advanced age is a predictor of poor prognosis after RC. The risk of recurrence was significantly higher in patients older than 80 years of age compared with those younger than 60 years [163]. The higher the age, the higher the number of pathologic stages and the more difficult it was to receive adjuvant therapy. In multivariate analysis, age was also an independent predictor of cancer-specific survival [163, 164].

Obesity is also associated with the prognosis of bladder cancer. Obesity was significantly correlated with recurrence (HR = 1.76, 95% CI: 1.36–2.28) but not with survival rate [165]. The risk of recurrence of obese population was 1.76 times higher than normal weight population. The risk of recurrence increased by 1.3% as BMI increased by 1 kg/m$^2$ [165]. The cause is not known exactly, but insulin resistance is presumed to be the main cause [166].

In patients with LVI, the risk of recurrence is 1.5 times higher than in patients without LVI. Cancer-specific mortality was also 1.5 times higher [167]. Several studies have reported that LVI is a predictor of LN metastasis. This suggests that LVI may be associated with hematologic tumor spread [168, 169].

Histologic variant has a worse prognosis than pure urothelial cancer [170]. The micropapillary type is reported to have poor cancer-specific survival, and the 5-year survival rate is 50% [169]. Sarcomatoid type is seen in high stage and grade and is accompanied by lymph node metastasis, and the 2-year survival rate is <30% [171]. The small cell type has a 5-year survival rate of <40%. Plasmacytoid type is mostly found in the presence of metastasis [170].

### 10.9.4 Urethral Recurrence After Neobladder Formation

In patients with radial cystectomy, recurrence in the urethra is <8% on average [172]. The incidence of males is higher than females. Most urethral recurrence usually recurs within the first 2 years after radical cystectomy [172].

Related factors of urethral recurrence include vaginal wall invasion, prostate invasion, bladder neck involvement, tumor multifocality, and diversion type [172]. The risk of urethral recurrence of the neobladder type rather than the cutaneous diversion type [172].

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# 11

# Multimodality Therapy

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## 11.1 Overview of Multimodality Therapy Approaches

### 11.1.1 Introduction

Radical cystectomy with pelvic lymph node dissection has been the gold standard management for muscle-invasive bladder cancer (MIBC). However, removal of the bladder may cause morbidity and have substantial effect on quality

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of life. In spite of several methods of bladder-preserving options, a trimodal therapy (TMT) approach has generally superior outcomes. TMT includes the chemotherapy, radiation therapy (RT), and transurethral resection of bladder tumor (TURB). TMT provides comparable 5-year overall survival to radical cystectomy.

### 11.1.2 Patient Selection

To select patients appropriately, first, patients' bladder function should be adequate to warrant preservation. If maximal tumor resection due to extensive tumors restricts bladder capacity, patients would not enjoy an improvement in bladder function. Second, the disease should be appropriate for TMT. Success rate is associated with some clinicopathological features that are further described below. Third, surgical extirpation should be a possible option for salvage therapy in case of unsuccessful TMT. Patients inappropriate for cystectomy could be managed with definitive chemoradiation.

### 11.1.3 Split Course or Continuous Course

The basic tactics of TMT is a combination of TURB with concurrent chemotherapy and RT. Both courses are initiated with maximal TURB. Cystoscopic examination with biopsy of the prior tumor lesion is conducted after completion of TMT (continuous course) or early after induction of TMT (split course) [1]. Immediate radical cystectomy is needed in patients with incomplete response. Radiation dose of induction therapy and consolidation are 40 Gy and continue to a full dose of about 65 Gy in most trials [2].

In split course, 40 Gy induction radiation with concurrent chemotherapy is conducted after maximal TURB. Then biopsies are performed under cystoscopic examination. In incomplete response case, salvage cystectomy is needed, and in complete response case, 65 Gy full-dose consolidation radiation with concurrent chemotherapy is conducted followed by surveillance.

In continuous course, full-dose radiation with concurrent chemotherapy is conducted after maximal TURB. Then biopsies are performed under cystoscopic examination. In incomplete response case, salvage cystectomy is needed, and in complete response case, just surveillance is recommended.

### 11.1.4 Radiation Regimens

Comparing twice- with once-daily radiations, fractionation was not a prognostic factor [2, 3]. Whether pelvic nodal packets are included in target volume or not differed among studies [2, 4]. Nonetheless, most regimens included radiation to a limited pelvic region because regional nodal involvement is common in muscle-invasive disease. Limiting the size of nodal field dose (40–45 Gy) may lead to potential prevention of later urinary diversions with small bowel [5].

Daily soft tissue computed tomography (CT)-guided setup for radiation was reported as superior to kilovoltage portal positioning according to bony or skin alignment in bladder cancer and reported to decrease toxicity after treatment [6]. Nowadays, the radiation protocol preserving the bladder includes external-beam radiation therapy with 40 Gy initially to the bladder and limited pelvic lymph nodes, 54 Gy of a boost to whole bladder, and a total dose of 64–65 Gy for a further tumor boost [7].

### 11.1.5 Chemotherapy Regimens

The most effective agent for advanced or metastatic disease is cisplatin [8]. Radiosensitizing properties of cisplatin are substantial for combined-modality therapies [9]. Different schedules and intensification of cisplatin resulted in no significant benefit of response rates [10, 11]. However, considerable proportion of patients with decreased kidney function, a cisplatin-based chemotherapy is not fit for all patients. Mitomycin C (MMC) plus 5-fluorouracil (5-FU)-based regimen for patients inappropriate for a cisplatin-based chemotherapy was proved to have radiosensitizing effect with tolerable toxicity [12]. The concurrent MMC/5-FU chemotherapy with radiation has been reported by a randomized phase 3 trial. The risk of locoregional recurrence and invasive recurrence was reduced 33% and 50% that was associated with the addition of the regimen [13].

## 11.2 Oncologic Results

### 11.2.1 Response Rate

Most studies defined complete response as the absence of tumor cells in the urine cytology, pathologically proven tumor on biopsy and visible tumor. According to Ploussard et al., the overall mean response rate was 73% after TMT [1]. Patients with complete response to induction showed better survival rates than patients with failure of complete response by one-third.

### 11.2.2 Survival

The 5-year disease-specific survival was between 50 and 82% [1]. The 5-year overall survival ranged from 36 to 74% [1]. Differences between cancer-specific survival and overall survival may be due to patient selection, the era of inclusion, duration of follow-up, differences in chemoradiation regimens, and so on. The British Columbia Cancer Agency reported their experience [14]. The 5-year and 10-year disease-specific survival were 31% and 27%. The 5-year and 10-year overall survival were 30% and 17%. According to the most recent systematic review and meta-analysis, TMT showed 30.9 and 50.9% of the mean 10-year overall survival and the mean 10-year disease-specific survival [15].

### 11.2.3 Predictors of Response

Selecting candidates for TMT is important because 5-year cancer-specific survival rate was worse in nonresponders than in responders [1]. Hydronephrosis has been reported as a poor prognostic factor, and RTOG protocols have excluded cases with hydronephrosis caused by tumor since 1993. Hydronephrosis which existed in 10–35% of eligible patients was associated with worse outcomes. Maximal TURB is a definitive prognostic factor. Complete TURB resulted in a 20% improvement in complete response [2]. In several studies, patients with insufficiency of complete TURB were excluded [16, 17]. Most investigations considered incomplete TURB is associated with worse response rates and survival outcomes. High clinical stage, high tumor grade, and lymph node involvement, as in radical cystectomy series, have been prognostic factors for worse outcomes in patients managed with TMT [18, 19].

## 11.3 The Experience of RTOG/MGH

The Radiation Therapy Oncology Group (RTOG) has conducted series of protocols. Most of these patients' enrollment and protocol development were performed at the Massachusetts General Hospital (MGH). Between 1986 and 2013, 475 patients were enrolled with a median follow-up of 7.2 years for survivors [20]. With improvements in radiation, chemotherapy, and surgery, significant improvements of rates of complete response (CR) to chemoradiation, overall survival (OS), disease-specific survival (DSS), and bladder-intact DSS were detected among different eras (1986–1995, 1996–2004, 2005, 2013).

TMT protocols assessed neoadjuvant/adjuvant chemotherapy, daily vs. twice radiation, and different regimens of radiation-sensitizing chemotherapy. Radiation to the tumor was 64–66 Gy maximally. Generally concurrent cisplatin-based chemotherapy and radiation therapy after maximal TURB are performed. Initial tumor response was evaluated by biopsy after 40 Gy. Patients with complete response or Ta or CIS then underwent consolidation with additional chemoradiation with a total of 64–65 Gy. Then close surveillance with cystoscopic examination and immediate salvage cystectomy for invasive recurrence or tumor persistence were performed. The most recent protocols used adjuvant chemotherapy (combination of cisplatin and gemcitabine) for all patients.

The current standard consists of maximal TURB followed by induction. The induction is twice-daily radiation over 26 fractions to 40.3 Gy. Concurrently cisplatin (15 mg/m$^2$ on days 1–3, 8–10, 15–17) and continuous infusion 5-FU (400 mg/m$^2$ on days 1–3, 15–17) were conducted. Patients who underwent postinduction TURB downstaged to T0, CIS, or Ta disease culminate in consolidation. Consolidation is twice-daily radiation to a total of 64.3 Gy. Concurrently the same regimen of induction chemotherapy was conducted. In case of no evidence of MIBC at postconsolidation TURB, four cycles of cisplatin (70 mg/m$^2$ on day 1 of 21-day cycles) and gemcitabine (1000 mg/m$^2$ on days 1 and 8 of 21-day cycles) were performed as adjuvant chemotherapy.

The most recent update showed 75%, 13.6%, and 13.4% of patients achieved complete response after induction therapy, incomplete response after induction therapy, and recurrent invasive tumors on follow-up. Disease-specific survival rates were 66%, 59%, and 56% at 5, 10, and 15 years. Overall survival rates were 57%, 39%, and 25% at 5, 10, and 15 years. Bladder-intact disease-specific survival rates were 52%, 46%, and 40% at 5, 10, and 15 years.

Several factors associated with oncologic outcomes were identified by multivariate analyses. Among patients with visibly complete TURB, 24% underwent cystectomy, while 43% required cystectomy in incomplete TURB group ($p < 0.001$). In analysis for overall survival, incomplete TURB, tumor-associated CIS, hydronephrosis, incomplete response, clinical T stage, and age at diagnosis were significant predictors. For disease-specific survival, incomplete response, clinical T stage, and tumor-associated CIS were significant.

## 11.4 Recurrence and Salvage Therapy After TMT

### 11.4.1 Recurrence

Like other bladder cancer treatments, bladder preservation treatments for MIBC had the risk of recurrence. The rate of local cancer recurrence among patients who had complete remission (CR) after TMT induction was 27–40.4% [21, 22]. At the study of Tsukuba University, intravesical recurrence rate without metastasis was 22.1%, and recurrence with metastasis was 6.5%. Of intravesical recurrences, recurrence rate was observed 18.2% of NMIBC type and 3.9% of MIBC type. In the NMIBC cases, the median time to recurrence was earlier than MIBC (29.7 months vs. 14.1 months) [23]. Efstathiou et al. noted that 10-year recurrence rates were 29%, 16%, 11%, and 32% of noninvasive, invasive, pelvic (nodal and sidewall), and distant. Of these recurrent tumors, MIBC recurrence rates were between 11 and 18.5% among patients who had CR [2].

### 11.4.2 Salvage Therapy After TMT

Salvage cystectomy is recommended when bladder preservation treatment (BPT) fails. The probability of performing salvage cystectomy varied from study to study due to differences in treatment protocol. According to several studies, including early cystectomy for patients with no response to TMT and delayed cystectomy for invasive recurrence, rates of salvage cystectomy were reported in 15–28% within 5 years [17, 24, 25].

Generally, when salvage cystectomy is performed after TMT, urologists are worried that the outcomes and complications of surgery are associated with radiotherapy. That worry is about tissue healing like anastomosis, wound, stomal stenosis, and gastrointestinal (GI) problems. In recent several analyses, major complications and perioperative mortality after salvage cystectomy are not different from those after primary radical cystectomy [26, 27].

Eswara et al. noted that early salvage cystectomy was underwent in 55% patients of nonresponder, and delayed salvage cystectomy was underwent in 45% patients of invasive recurrence. With median 12-year follow-up, loop diversion was conducted in 99% for salvage cystectomy. In this study, major complication, Clavien grades 3–5, was occurred in 16% patients, and mortality rate was 2.2% within

90 days. They also compared complication rates of early cystectomy and delayed cystectomy within 90 days. Early cystectomy showed 37% of major complication, 12% of tissue healing complications and delayed cystectomy showed 15%, 35% for each complication [26].

## 11.5 Comparison TMT vs. RC

### 11.5.1 Survival

A comparative study of radical cystectomy (RC) and bladder preservation treatment (BPT) using randomized controlled trial is insufficient. Because of differences in treatment timing and pathologic stage after RC, direct comparison is difficult. But in a limited study, bladder preservation treatment with TMT has shown a similar survival outcome compared with RC (Table 11.1). TMT can be considered as a reasonable treatment option in well-selected patients.

The results of the RC series showed that the 5-year OS rates were 58–62% and 5-year recurrence-free survival (RFS) rates were 60–66% [32, 33]. By comparison, Efstathiou et al. reported that 5-year OS rates were 57% for patients who received complete TUR and 43% for patients who received incomplete TUR [2]. Azuma et al. conducted a study for comparing RC and BPT. In their study, 62 patients received RC and other 62 patients received BPT. BPT group showed a higher OS rates than RC group. In the RC group, the overall 15-year survival rate was 40%, but in the BPT group, the overall 14-year survival rate was 79.7% [34]. AlGizawy et al. [35] conducted a comparison study with 80 patients of RC arm and 80 patients of BPT arm for invasive nonmetastatic bladder cancer, T2-3. As a result, RC arm and BPT arm have no significant difference in OS, DSS, and progression-free survival for 3-year follow-up.

### 11.5.2 Bladder Function and Quality of Life

Conservation of native bladder and cosmetics is the main reason to choose to treat the bladder cancer and to continue to study TMT therapy. Unlike urinary diversion surgery, preservation of the bladder can be expected to maintain the function and to improve quality of life (QoL) of the bladder. For an evaluation of function and QoL, some studies on these two topics during the long-term follow-up were conducted through the urodynamic study (UDS) and the questionnaire.

Thirty-two patients participated in the questionnaire and UDS test for QoL and bladder function analysis in a MGH study [36]. Of the 18 male patients, 5 showed impaired compliance of the bladder, but they had normal voiding and storage function on UDS. Of the ten female patients, two showed impaired compliance of the bladder, increased bladder sensation, and involuntary detrusor contractions. With median follow-up time of 6 years, 75% revealed normal bladder function. One-third of 22% patients who had reduced bladder compliance complained of distressing bladder symptoms. Totally 25% of the patients complained that nocturia was the most troublesome symptom. Seven men (20%) and three women (27%) com-

**Table 11.1** Comparison of survival outcomes of radical cystectomy and multimodal treatment in contemporary series

| Study | No. of patients | Stage | Treatment method | Outcomes |
|---|---|---|---|---|
| USC [28] | 633 | pT2-4a | RC | 5-year OS: 48%<br>10-year OS: 32% |
| MSKCC [29] | 181 | pT2-4a | RC | 5-year OS: 36%<br>10-year OS: 27% |
| SWOG/ECOG/CALGB [30] | 303 | cT2-3 | RC | 5-year OS: 49%<br>10-year OS: 34% |
| BC2001 [13] | 182 | cT2-4a | MMT | 5-year OS: 49% |
| RTOG [31] | 468 | cT2-4a | MMT | 5-year OS: 57%<br>10-year OS: 36% |
| MGH [20] | 475 | cT2-4a | MMT | 5-year OS: 57%<br>10-year OS: 39% |

plained of bowel control difficulty that was a major symptom after bladder preservation treatment. Of the male patients, 54% were able to have a sufficient erection to penetrate the vagina. Mak et al. compared the QoL of RC and TMT in long-term survivors. In their study, TMT showed significantly higher scores in general QoL, physical, role, emotional, social, and cognitive functioning on the questionnaire than RC [37].

### 11.5.3 Treatment-Related Toxicity

Although the above studies have reported acceptable survival rates, it is true that there are concerns about complications after TMT treatment. Concerns are mainly related to the effect of tissue by radiation, including urinary function, GI problem, and sexual functions, which include partly similar kind of concerns as post-salvage cystectomy complications.

During the chemoradiotherapy, side effects that patients commonly experienced are diarrhea, fatigue, nausea, and urinary symptoms [13]. Additionally, chemotherapy drug like cisplatin, 5FU, and mitomycin C could occur damage of the kidney and sensory with risk of increasing toxicity grade. Efstathiou et al. reported late pelvic toxicity after BPT with median follow-up of 5.4 years [5]. Of the 157 patients, 11 (7%) patients experienced grade 3 late toxicity. Nine (5.7%) had genitourinary complication and three (1.9%) had GI complications. However, none of the patients showed grade 4 toxicity.

## 11.6 Conclusion

It was shown that BPT treatment was an effective modality in patients with MIBC who wish to preserve the bladder. There is no RCT comparison yet, in the cumulative studies; if the patient is selected appropriately and maximal TUR is performed, BPT is an alternative treatment for radical Cx. Long-term follow-up studies have reported that TMT shows good results in local control of bladder cancer, recurrence rates, complications associated with treatment, and quality of life. Therefore, MMT can be suggested to patients who are not eligible for surgical treatments due to age, underlying disease, or socioeconomic problems, as well as patients who wish to preserve their bladder in less aggressive ways. In the MMT protocols, it is important to cooperate in urology, radiation oncology, and medical oncology to coordinate each modality of treatments and to continuously assess disease course.

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# 12

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## 12.1 Pretreatment Evaluation

It is important to understand the condition of the patient before treatment in palliative chemotherapy. Therefore, the overall medical problem and physiologic considerations including performance status, renal function, and cardiac function should be evaluated. Based on this, risk classification and treatment options are determined. Cisplatin-based combination chemotherapy is the standard regimen of metastatic bladder cancer. However, cisplatin-based combination chemotherapy has potential nephrotoxicity. Therefore, it is important to evaluate the renal function. It is also important to assess the age, urinary tract obstruction, single kidney, and smoking vascular disease that may be risk factors for kidney damage [1]. Reversible causes of renal impairment such as bladder cancer-related urinary tract obstruction should be treated before cisplatin-based combination chemotherapy. In order to attempt and develop a consensus definition for patients not eligible for chemotherapy (panel) using cisplatin in patients with

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**Table 12.1** Inadequate conditions for cisplatin-based chemotherapy

| Inadequate conditions |
|---|
| Eastern Cooperative Oncology Group (ECOG) performance status ≥2 |
| Karnofsky performance status ≤60% |
| Creatinine clearance (CCr) <60 mL/min |
| Hearing loss (measured at audiometry) of 25 dB at two contiguous frequencies |
| Peripheral neuropathy ≥ grade 2 |
| Heart failure ≥ New York Heart Association class III |

**Table 12.2** Eastern Cooperative Oncology Group (ECOG) performance status definitions [3]

| Performance status | Definition |
|---|---|
| 0 | Fully active; no performance restrictions |
| 1 | Strenuous physical activity restricted; fully ambulatory and able to carry out light work |
| 2 | Capable of all self-care but unable to carry out any work activities; up and about at least 50% of waking hours |
| 3 | Capable of only limited self-care; confined to bed or chair at least 50% of waking hours |
| 4 | Completely disabled; cannot carry out any self-care; totally confined to bed or chair |

metastatic UC, a working group of genitourinary medical oncologists was constructed. Consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. Patients meeting at least one of the following are considered “unfit” (Table 12.1) [2]: ECOG (Eastern Cooperative Oncology Group) 2 or higher (Tables 12.1 and 12.2) or Karnofsky status 60–70% or less (Table 12.3); creatinine clearance less than 60 mL/min; hearing loss at two adjacent frequencies (measured at hearing) is 25 dB; peripheral neuropathy of grade 2 or higher (e.g., sensory alteration or paresthesia, including tingling, that does not interfere with activities of daily living); and New York Heart Association class III or greater heart failure [2]. If only one of the above criteria is not met, cisplatin-based combination therapy may be performed.

**Table 12.3** Karnofsky performance status scale [4]

| Percentage of functional capacity | General performance status | Criteria |
|---|---|---|
| 100 | Normal, no complaints, no evidence of disease | Able to carry on normal activity and to work; no special care needed |
| 90 | Able to carry on normal activity, minor signs or symptoms of disease | |
| 80 | Normal activity with effort, some signs or symptoms of disease | |
| 70 | Cares for self; unable to carry on normal activity or to do active work | Unable to work; able to live at home and care for most personal needs; various degrees of assistance needed |
| 60 | Requires occasional assistance but is able to care for most needs | |
| 50 | Requires considerable assistance and frequent medical care | |
| 40 | Disabled; requires special care and assistance | Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly |
| 30 | Severely disabled; hospitalization is indicated although death is not imminent | |
| 20 | Hospitalization is necessary; very sick; active supportive treatment necessary | |
| 10 | Moribund; fatal processes progressing rapidly | |
| 0 | Dead | |

However, patients who cannot receive cisplatin can consider carboplatin-based therapy (e.g., carboplatin + gemcitabine), non-platinum-based therapy (e.g., paclitaxel + gemcitabine) or monotherapy chemotherapy (Table 12.4).

**Table 12.4** Chemotherapy regimens according to cisplatin eligibility

| | Standard regimens | Alternative regimens |
|---|---|---|
| Cisplatin eligible | GC<br>DDMVAC | |
| Cisplatin ineligible | Gemcitabine + carboplatin | Gemcitabine<br>Gemcitabine + paclitaxel |

## 12.2 First-Line Chemotherapy

Systemic cisplatin-based chemotherapy is a standard treatment for patients with metastatic urothelial cancer of the bladder and urinary tract [5]. Table 12.5 shows that first-line chemotherapy regimens include DDMVAC, GC, and PGC.

**Table 12.5** First-line chemotherapy regimens include DDMVAC, GC, and PGC

| Regimen | Dosing |
|---|---|
| DDMVAC with growth factor support [6, 7] | Day 1: Methotrexate 30 mg/$m^2$ IV |
| | Day 2: Vinblastine 3 mg/$m^2$ IV plus doxorubicin 30 mg/$m^2$IV plus cisplatin 70 mg/$m^2$ IV |
| | Day 4: G-CSF 240 μg/$m^2$ SQ injection for 7 consecutive days (days 4 through 10). May be extended for up to a total of 14 consecutive days |
| | Repeat every 2 weeks |
| Gemcitabine + cisplatin (GC) [8–10] | Days 1, 8, and 15: Gemcitabine 1000 mg/$m^2$ IV over 30–60 min |
| | Day 2: Cisplatin 70 mg/$m^2$ |
| | Repeat every 4 weeks |
| Paclitaxel + gemcitabine + cisplatin (PGC) | Day 1: Paclitaxel 80 mg/$m^2$ IV plus gemcitabine 1000 mg/$m^2$ IV plus cisplatin 70 mg/$m^2$ IV |
| | Day 8: Paclitaxel 80 mg/$m^2$ IV plus gemcitabine 1000 mg/$m^2$ IV |
| | Repeat every 3 weeks |

### 12.2.1 Baseline Studies on the Effectiveness of Chemotherapy for Metastatic Bladder Cancer

In the intergroup randomized comparative study, both GC and MVAC were significant in response rate and overall survival [8]. MVAC was superior in efficacy and GC in toxicity [11]. In another study, the response rate, progression time, and overall survival rate of GC and MVAC were similar [12]. It was confirmed the equivalence of the two drugs and reported good tolerability in the GC drug group. And the tolerability of the GC group was good. In 63% of patients with MVAC, a dose change was required [11, 12]. In GC patients, only 25% experienced grade 3 toxicity [11, 12].

#### 12.2.1.1 Methotrexate, Vinblastine, Doxorubicin, and Cisplatin

GC and MVAC are most commonly used in cisplatin-based combination chemotherapy regimens. MVAC has become the first standard therapy for bladder cancer based on the results of a phase II and III randomized controlled trial demonstrating improved survival results (Table 12.6) [13, 17]. The combined complete and partial response rate was significantly higher for patients treated with MVAC than for those treated with cisplatin, cyclophosphamide, and Adriamycin (CISCA) (65% vs. 46%; $P > 0.05$). The survival duration of MVAC-treated patients was significantly longer than that of CISCA-treated patients (mean, 62.6 weeks; median, 48.3 vs. mean, 40.4 weeks; median, 36.1) [13, 17].

In a large randomized phase III trial comparing high-dose (HD) intensity MVAC and classic MVAC [7] (Table 12.7), HD-MVAC arm, there were 28 complete responses (CRs) (21%) and 55 partial responses (PRs) (41%), for an overall response of 62%. On the MVAC arm, there were 12 CRs (9%) and 53 PRs (41%), for an overall response of 50%. The $P$ value for the difference in CR rate was 0.009; and for the overall response,

**Table 12.6** Key phase III trial results of cisplatin-based combination chemotherapy

| Regimen | Complete response (%) | Response rate (%) | Medial progression-free survival (months) | Median overall survival (months) | References |
|---|---|---|---|---|---|
| MVAC | 12–35 | 39–65 | 7.4–10.0 | 12.5–14.8 | [2, 11, 13, 14] |
| GC | 12 | 49 | 7.4 | 13.8 | [11] |
| CMV | 10 | 36 | NA | 7.0 | [15] |
| PGC | 13.5 | 55.5 | 8.3 | 15.8 | [16] |

**Table 12.7** Randomized clinical trials of chemotherapy in metastatic bladder cancer

| Study | No. of patients | Neoadjuvant arm | Relative risk | Median survival | *P* value |
|---|---|---|---|---|---|
| Intergroup [13] | 269 | MVAC/cisplatin | 39 vs. 12 | 12.5 vs. 8.2 | <0.001 |
| MDAH [17] | 110 | MVAC/CISCA | 65 vs. 46 | 11.1 vs. 8.3 | <0.001 |
| EORTC [18] | 263 | DDMVAC/MVAC | 72 vs. 58 | 14.9 vs. 15.1 | 0.041 |
| Lilly [8] | 405 | GC/MVAC | 49 vs. 46 | 14.0 vs. 15.2 | 0.66 |
| Greece [19] | 220 | DC/MVAC | 37 vs. 54 | 9.3 vs. 14.2 | 0.026 |
| EORTC [16] | 626 | GC/PCG | 46 vs. 57 | 12.7 vs. 15.8 | 0.03 |

it was 0.06. There was no statistically significant difference in survival ($P = 0.122$) or time to progression ($P = 0.114$). Progression-free survival was significantly better with HD-MVAC ($P = 0.037$). The median progression-free survival time was 9.1 months on the HD-MVAC arm versus 8.2 months on the MVAC arm. The 2-year progression-free survival rate was 24.7% for HD-MVAC versus 11.6% for MVAC. Although a 50% difference in median overall survival was not detected, the National Comprehensive Cancer Network (NCCN) guidelines include HD-MVAC instead of the standard MVAC as a category 1 recommendation for first-line chemotherapy. The main concern of MVAC therapy is related to toxicity, which requires dose adjustment in most patients with bladder cancer. The toxic death rate was 1% on the GC arm and 3% on the MVAC arm [11]. More MVAC patients, compared with GC patients, had grade 3/4 neutropenia (82% vs. 71%), neutropenic fever (14% vs. 2%), neutropenic sepsis (12% vs. 1%), and grade 3/4 mucositis (22% vs. 1%) and alopecia (55% vs. 11%) [11]. Treatment with human recombinant granulocyte colony-stimulating factor (rhG-CSF) before chemotherapy resulted in a dose-dependent increase in the absolute neutrophil count. Treatment with rhG-CSF after chemotherapy considerably reduced the number of days (91%) per patient and reduced the number of days (1 vs. 35) on which antibiotics were used to treat fever and neutropenia. In addition, the incidence of mucositis was significantly decreased (11 vs. 44%, $P = 0.041$), as was its severity [20, 21]. Due to the complications associated with these treatments, despite the NCCN recommendations, some experts prefer the standard MVAC over HD-MVAC.

#### 12.2.1.2 Gemcitabine and Cisplatin

In a phase II studies about weekly gemcitabine and cisplatin combination therapy, there were 18% of complete and 24% partial responses, for a response rate of 42% [22, 23]. Median response duration was 13.5 months, median time to progressive disease 7.2 months, and median survival 12.5 months; 1-year survival was 52% [22, 23]. Toxicities included leukopenia (44% grade 3; 17% grade 4), neutropenia (25% grade 3; 33% grade 4), and thrombocytopenia (29% grade 3; 49% grade 4). There were no grade 4 infections and no toxic deaths [22, 23]. In phase III studies comparing GC and MVAC, overall survival was similar in both arms (hazard ratio [HR], 1.09; 95% CI, 0.88–1.34; $P = 0.66$) with a median survival of 14.0 months for GC and 15.2 months for MVAC [8, 11]. The 5-year overall survival rates were 13.0% and 15.3%, respectively ($P = 0.53$)

[8, 11]. The median progression-free survival was 7.7 months for GC and 8.3 months for MVAC. The 5-year progression-free survival rates were 9.8% and 11.3%, respectively ($P = 0.63$). The 5-year overall survival rates for patients with and without visceral metastases were 6.8% and 20.9%, respectively [8, 11]. However, there were fewer 3/4 toxicities such as neutropenia (71% vs. 82%), neutropenic sepsis (2% vs. 14%), and mucositis (1% vs. 22%). Patients who received GC had greater weight gain, less fatigue, and better performance status than patients who received MVAC. GC with similar efficacy and low toxicity is considered to be the first chemotherapy for metastatic bladder cancer rather than MVAC. Alternative 3-weekly dosing schedules of the GC regimen were studied and were similar to the 28-day regimens [23–25].

#### 12.2.1.3 Paclitaxel, Gemcitabine, and Cisplatin

EORTC 30987 trial was a randomized phase III study to compare paclitaxel/cisplatin/gemcitabine (PCG) with GC in patients with locally advanced or metastatic urothelial carcinoma [16]. 626 patients were randomly assigned; 312 patients were assigned to PCG, and 314 patients were assigned to GC. After a median follow-up of 4.6 years, the median OS was 15.8 months on PCG versus 12.7 months on GC. OS in the subgroup of all eligible patients was significantly longer on PCG (3.2 months; HR, 0.82; $P = 0.03$), as was the case in patients with bladder primary tumors. PFS was not significantly longer on PCG (HR, 0.87; $P = 0.11$). Overall response rate was 55.5% on PCG and 43.6% on GC ($P = 0.0031$). Both treatments were well tolerated, with more thrombocytopenia and bleeding on GC than PCG (11.4% vs. 6.8%, respectively; $P = 0.05$) and more febrile neutropenia on PCG than GC (13.2% vs. 4.3%, respectively; $P < 0.001$). Compared to the GC group, these results suggest that PGC is a treatment option for patients with metastatic urinary tract carcinoma and should be used for patients with primary cancer origin bladder.

### 12.2.2 Chemotherapy for Cisplatin-Ineligible Patients

EORTC 30986 trial was the first randomized phase II/III trial comparing two carboplatin-based chemotherapy regimens in patients with urothelial cancer who are ineligible for cisplatin chemotherapy [26]. The trial was consisted of chemotherapy-naïve 238 patients with measurable disease and an impaired renal function (glomerular filtration rate <60 but >30 mL/min) and/or performance score of 2 who were randomly assigned to receive either gemcitabine/carboplatin (GC) or methotrexate/carboplatin/vinblastine (M-CAVI) [26]. The median follow-up was 4.5 years. Best objective response rates (ORRs) were 41.2% (36.1% confirmed response) for patients receiving GC versus 30.3% (21.0% confirmed response) for patients receiving M-CAVI ($P = 0.08$). Median OS was 9.3 months in the GC arm and 8.1 months in the M-CAVI arm ($P = 0.64$). There was no difference in PFS ($P = 0.78$) between the two arms. Severe acute toxicity (death, grade 4 thrombocytopenia with bleeding, grade 3 or 4 renal toxicity, neutropenic fever, or mucositis) was observed in 9.3% of patients receiving GC and 21.2% of patients receiving M-CAVI. These results support use in patients with poor renal function or with poor performance status (ECOG $\geq 2$) with concurrent therapy or chemotherapy. In phase II trial on weekly paclitaxel and gemcitabine in patients with advanced transitional-cell carcinoma, 69.4% of patients had major responses to treatment, including 41.7% with complete responses [27]. With a median follow-up time of 38.7 months, the median survival time was 15.8 months. Grade 3 and 4 toxicities included granulocytopenia (36.1%), thrombocytopenia (8.3%), and neuropathy (16.7%). 13.9% had grades 3–5 pulmonary toxicity, and 1 patient had grade 2 pulmonary toxicity [27]. In another phase II trial of combination chemotherapy with paclitaxel and gemcitabine in patients with advanced transitional cell carcinoma, 54% of patients had major responses to treatment, including 7% complete responses [28]. With a median follow-up of 24 months, 30% remain alive, and

17% are progression-free with a median follow-up of 24 months. The median survival for the entire group was 14.4 months. 47% previously treated with platinum-based chemotherapy responded to paclitaxel/gemcitabine. Grade 3/4 toxicity was primarily hematologic, including leukopenia (46%), thrombocytopenia (13%), and anemia (28%) [28]. The combination of paclitaxel and gemcitabine was tolerable in patients with advanced transitional cell carcinoma.

## 12.3 Second-Line Chemotherapy

Although they have a response rate of 40–60% of first-line chemotherapy, most patients with metastatic bladder cancer show progression within 1 year. In this case, a second choice of chemotherapy is needed. However, in the case of second-line chemotherapy, standard therapy does not exist unlike the first-line chemotherapy. There is also no standard starting time and duration of second-line chemotherapy treatment. In a randomized phase III study of vinflunine (VFL) and best supportive care (BSC) versus BSC alone in the treatment of patients with advanced transitional cell carcinoma who had experienced progression after a first-line platinum-containing regimen, the objective of a median 2-month survival advantage (6.9 months for VFL + BSC vs. 4.6 months for BSC) was achieved but was not statistically significant ($P = 0.287$) [29]. Multivariate Cox analysis adjusting for prognostic factors showed statistically significant effect of VFL on OS ($P = 0.036$), reducing the death risk by 23%. In the eligible population, the median OS was significantly longer for VFL + BSC than BSC (6.9 vs. 4.3 months, respectively), with the difference being statistically significant ($P = 0.040$). Overall response rate, disease control, and progression-free survival were all significant favoring VFL + BSC ($P = 0.006$, $P = 0.002$, and $P = 0.001$, respectively) [29]. Both arms were well balanced except there were more patients with PS more than 1 (10% difference) in the BSC arm. Main grade 3 or 4 toxicities for VFL + BSC were neutropenia (50%), febrile neutropenia (6%), anemia (19%), fatigue (19%), and constipation (16%) [29]. Vinflunine has been approved as a second-line treatment for urothelial cancer in Europe, but has not been approved in the United States due to lack of statistical significance for OS. Therefore BSC remains a feasible approach in the second-line setting, especially in patients with poor performance status.

### 12.3.1 Changed to Other Cisplatin-Based Chemotherapy Regimens

If the patient is suitable for cisplatin treatment even after first-line chemotherapy, treatment with another cisplatin-based regimen is possible. In a phase II clinical trial, the response rate and CR rate were reported to be 30% and 6.7%, respectively, when using MVAC as a second-line chemotherapy regimen in patients with GC failure [30]. The overall disease control rate was 50%. Seven out of 16 patients who had responded previously to GC responded to MVAC, while 2 out of 14 who had not responded to GC responded to MVAC [30]. The median response duration was 3.9 months, and the median progression-free survival was 5.3 months [30]. The median overall survival was 10.9 months [30]. The major toxicities were neutropenia and thrombocytopenia. A grade 3 or 4 neutropenia occurred in 19 patients (63.3%), and a grade 3 or 4 thrombocytopenia developed in 9 patients (30.0%). In another study enrolled 45 patients with advanced UC who received second-line MVAC chemotherapy after failure with first-line GP chemotherapy, the median PFS and overall survival (OS) were 6.5 months and 14.5 months, respectively [31]. The overall response rate was 57.8%. The response to first-line GP chemotherapy and patient age were predictors of PFS after MVAC chemotherapy [31].

### 12.3.2 Non-cisplatin-Based Chemotherapy Regimens

There have been many studies on single-agent second-line chemotherapy such as pemetrexed, vinflunine, paclitaxel, docetaxel, gemcitabine,

**Table 12.8** Phase II and phase III trials of second-line chemotherapy for urothelial carcinoma

| Agents | Phase | Year | N | ORR (%) | PFS (months) | OS (months) | References |
|---|---|---|---|---|---|---|---|
| Vinflunine | II | 2006 | 51 | 18 | 3.0 | 6.6 | [32] |
| Vinflunine | II | 2009 | 151 | 15 | 2.8 | 8.2 | [33] |
| Vinflunine | III | 2009 | 253 | 9 | 3.0 | 6.9 | [29] |
| Pemetrexed | II | 2006 | 47 | 28 | 2.9 | 9.6 | [34] |
| Pemetrexed | II | 2007 | 13 | 8 | NR | NR | [35] |
| Paclitaxel | II | 1997 | 14 | 7 | NR | NR | [36] |
| Paclitaxel (weekly) | II | 2002 | 31 | 10 | 2.2 | 7.2 | [37] |
| Docetaxel | II | 1997 | 30 | 13 | NR | 9.0 | [38] |
| Gemcitabine | II | 2002 | 30 | 11 | 4.9 | 8.7 | [39] |
| Gemcitabine | II | 2007 | 46 | 25 | 3.1 | 12.6 | [40] |
| Ifosfamide | II | 1997 | 56 | 20 | 2.4 | 5.5 | [41] |

ifosfamide, and oxaliplatin (Table 12.8). However, the overall response rate of the second-line single agents ranged from 5% to 20%, and the median PFS was 3–4 months [42]. Also, there was no evidence that secondary chemotherapy improves OS or quality of life [42]. Monotherapy was neither approved for use in patients with metastatic urinary tract carcinoma nor validated in phase III clinical trials of single agents.

#### 12.3.2.1 Vinflunine

In phase II trial of vinflunine as second-line therapy in patients with advanced transitional cell carcinoma, there was an overall response rate of 18%, and 67% achieved disease control (PR + SD) [32]. The median duration of response was 9.1 months, the median PFS was 3.0 months, and the median OS was 6.6 months [32]. The main hematological toxicity was grade 3–4 neutropenia, observed in 67% of patients. Febrile neutropenia was observed in five patients (10%), and among them two were fatal [32]. In another phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma, the median OS was significantly longer for VFL + BSC than BSC (6.9 vs. 4.3 months, respectively), with the difference being statistically significant ($P = 0.040$) [29]. Overall response rate, disease control, and progression-free survival were all statistically significant favoring VFL + BSC ($P = 0.006$, $P = 0.002$, and $P = 0.001$, respectively) [29].

#### 12.3.2.2 Pemetrexed

Pemetrexed is a novel, multi-targeted antifolate that is active in multiple tumor types [43]. In phase II study of pemetrexed for second-line treatment of transitional cell cancer, 6.4% of complete responses and 21.3% of partial responses produced an overall response rate of 27.7% [34]. 21.3% of patients had stable disease and 46.8% of patients progressed [34]. The median time to progressive disease was 2.9 months and median overall survival was 9.6 months [34]. Grade 3 or 4 hematologic complications were thrombocytopenia (8.5%), neutropenia (4.3%), and anemia (2.1%), respectively. In another single-center phase II study of pemetrexed administered as second-line therapy in patients with advanced urothelial carcinoma, overall response rate of 8% was reported, and 2/13 patients developed febrile neutropenia [35].

#### 12.3.2.3 Paclitaxel

Paclitaxel has already demonstrated quite significant single-agent activity in ovarian and breast cancer [44], as well as early results from a phase II study in previously untreated patients with advanced bladder cancer. In phase II study of paclitaxel in pretreated patients with locally advanced/metastatic cancer of the bladder and ureter, the response rates were one partial response (PR) (7%) and three stable diseases (SD) [45]. There were two early deaths. In another phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer, three patients achieved a 10% of partial response, 2.2 months of median time to progression, and 7.2 months of median overall survival time, and minimal hematologic toxicity was reported [37].

## 12.4 Novel Chemotherapeutic Agents

### 12.4.1 Molecular Targeted Agents

Urothelial carcinoma of the bladder is known to be the leading cause of morbidity and mortality worldwide and is reported to die 150,000 each year [46]. Molecular targeted agents have not been licensed as a new treatment for this disease. The Cancer Genome Atlas project that was included are data on DNA copy number, somatic mutation, messenger RNA and microRNA (miRNA) expression, protein and phosphorylated protein expression, DNA methylation, transcript splice variation, gene fusion, viral integration, pathway perturbation, clinical correlates, and histopathology to characterize the molecular landscape of urothelial carcinoma [47]. The project reported an integrated analysis of 131 urothelial carcinomas to provide a comprehensive landscape of molecular alterations. Up to 60% of high-grade urothelial carcinomas have potentially executable genetic alterations, particularly those involving the PI(3)K/AKT/mTOR, CDKN2A/CDK4/CCND1, and RTK/RAS pathways, including ERBB2 (HER-2), ERBB3, and FGFR3 [47, 48]. The following genetic alterations in urothelial carcinoma are potential drug targets: mutations in the receptor tyrosine kinases RAS and RAF, phosphoinositide 3-kinase/AKT/mammalian target of rapamycin pathways, regulators of G1-S cell cycle progression such as TP53 and RB1, fibroblast growth factor receptor (FGFR)-3 mutations and translocations, and amplifications in FGFR1, CCND1, and MDM2 genes.

### 12.4.2 Immune Checkpoint Inhibitors

Immune checkpoint inhibitors have recently begun to play an important role in metastatic bladder cancer treatment. The blockade of immune checkpoints that are able to enhance the immune response to tumors by restoring T-lymphocyte activation is the most notable modality among therapeutic modalities to activating antitumor activity [49]. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibodies were the first of this class to achieve a significant increase in survival for patients with metastatic melanoma [50]. And, one of the most actively studied is PD-1 (programmed cell death protein 1)/PD-L1 (PD-1 ligand) that is emerging as a promising target. PD-1 performs a role as inhibitory receptor regulating immune response at multiple levels and by different mechanisms. In recent, the blockade of PD-1 and PD-1 ligand in metastatic bladder cancer has showed improvement with an objective response rate and clinical benefit [51] (Table 12.9).

### 12.4.3 Biomarkers for Immunotherapy

#### 12.4.3.1 Atezolizumab

Expression of PD-L1 in metastatic urothelial cancer occurs at 20–30% [57]. The degree of PD-L1 expression in bladder tumors is known to be associated with an increased pathologic stage and mortality [58]. This means that there is higher PD-L1 expression in aggressive disease [59]. The end points associated with PD-L1 were analyzed in the clinical phase II and phase III studies of immunotherapy in urothelial cancer. An anti-PD-L1 monoclonal antibody atezolizumab (MPDL3280A) in the second-line treatment of metastatic bladder carcinoma was evaluated in phase I clinical trial (clinicaltrials.gov identifier: NCT1375842). Atezolizumab had 5% of grade 3–4 immune-mediated adverse events rate. And 53% of patients tested positive for anti-PD-L1 were evaluable for efficacy at time of analysis with a median follow-up of 14 months. Fifty percent of PD-L1-positive patients (IHC 2+ and IHC3+ assessed on immune cells) rapidly responded to immunotherapy with a median time to response of 62 days. The overall survival rate at 1 year was 57% in IC2/3 patients [51]. In multicenter, single-arm, two-cohort, phase II trial, the patients (aged ≥18 years) with inoperable

**Table 12.9** Approved of immune checkpoint inhibitors for platinum refractory advanced urothelial carcinoma

| Drug | Phase/no. of patients | ORR (%) | Median PFS/ OS (months) | Dosing | Grade 3/4 AEs (%) | Most common AEs | Target | FDA approval |
|---|---|---|---|---|---|---|---|---|
| Atezolizumab [52] | Phase II (310) | 15 | 2.1/7.9 | 1200 mg Q3W | 16 | Fatigue (30%)<br>Nausea (14%)<br>Decreased appetite (12%) | PD-L1 | May 18, 2016 |
| Nivolumab [53] | Phase II (265) | 20 | 2.0/8.7 | 3 mg/kg Q2W | 18 | Fatigue (17%)<br>Pruritus (9%)<br>Diarrhea (9%) | PD-1 | February 2, 2017 |
| Pembrolizumab [54] | Phase III (270) | 21 | 2.1/10.3 | 200 mg Q3W | 15 | Pruritus (19.5%)<br>Fatigue (13.9%)<br>Nausea (10.9%) | PD-1 | May 18, 2017 |
| Avelumab [55] | Phase Ib (241) | 18 | 1.5/7.0 | 10 mg/ kg Q2W | 8 | Infusion-related reaction (22.8%)<br>Fatigue (12.0%) | PD-L1 | May 9, 2017 |
| Durvalumab [56] | Phase I/II (191) | 18 | 2.2/18.2 | 10 mg/ kg Q2W | 7 | Fatigue (19.4%)<br>Decreased appetite (9.4%)<br>Diarrhea (8.4%) | PD-L1 | May 1, 2017 |

*Q3W* every 3 weeks; *Q2W* every 2 weeks

locally advanced or metastatic urothelial carcinoma whose disease had progressed after previous platinum-based chemotherapy received atezolizumab treatment [52]. The ORR was 15%, including a CR rate of 5% among all patients. The ORR was higher in patients with more expression of PD-L1 on infiltrating immune cells, and objective responses were sometimes observed in patients with no expression of PD-L1. Atezolizumab showed durable activity and good tolerability in this patient population. Increased levels of PD-L1 expression on immune cells were associated with increased response. The high expression of PD-L1 in atezolizumab-related IMvigor clinical trials predicted a high therapeutic response rate in phase I trials [51]. In phase II clinical trials, high expression of PD-L1 in immune cells was associated with increased OS with treatment with atezolizumab [52]. In the phase II clinical study, the Checkmate 275 study, the same immunofluorescent staining assay was used, but PD-L1 expression did not correlate with nivolumab treatment response [53].

#### 12.4.3.2 Other PD-1/PD-L1 Inhibitors

Monoclonal PD-1 antibody pembrolizumab was evaluated in another phase Ib study (clinicaltrials.gov identifier: NCT01848834). Pembrolizumab was proven to be stable and tolerable in advanced urothelial cancer. Overall response was 28%, and complete responses was 10%, median time to response was 9 weeks, and 1-year overall survival rate was 52.9% [60]. In the phase III clinical study, KEYNOTE-045 also showed no association between PD-1 expression in tumor and immune cells and tumor progression and disease progression and survival after treatment with pembrolizumab [61]. Monoclonal PD-1 antibody, nivolumab, alone or combined with monoclonal CTLA-4 antibody ipilimumab, was evaluated in phase I/II open-label study in patients with advanced or metastatic urothelial carcinoma (clinicaltrials.gov identifier: NCT01928394) (Table 12.10).

#### 12.4.3.3 Blocking CTLA-4

The first immune checkpoint receptor is CTLA-4. CTLA-4 play a role in downmodulation of helper T-cell activity and enhancement of regulatory T (TReg)-cell immunosuppressive activity. Blocking CTLA-4 results in a broad enhancement of effector CD4+ T-cell activity and inhibition of TReg cell-dependent immunosuppression [63]. Ipilimumab, monoclonal CTLA-4 antibody, was the first immune checkpoint blockade therapy to achieve the US Food and Drug Administration (FDA) approval in 2010 [50].

**Table 12.10** Approved of immune checkpoint inhibitors for first line of cisplatin-ineligible advanced urothelial carcinoma

| Drug | Phase/no. of patients | ORR (%) | Median PFS/OS (months) | Dosing | Grade 3/4 AEs (%) | Most common AEs | FDA approval |
|---|---|---|---|---|---|---|---|
| Atezolizumab [62] | Phase II (119) | 23 | 2.7/15.9 | 1200 mg Q3W | 16 | Fatigue (30%)<br>Diarrhea (12%)<br>Pruritus (11%) | April 17, 2017 |
| Pembrolizumab [61] | Phase III (370) | 29 | 2/NR | 200 mg Q3W | 19 | Fatigue (18%)<br>Pruritus (17%)<br>Rash (12%) | May 18, 2017 |

A phase II study (clinicaltrials.gov identifier: NCT01524991) is currently ongoing to evaluate the combination of ipilimumab with gemcitabine and cisplatin in first-line treatment of advanced or metastatic urothelial carcinoma.

## 12.4.4 Precision Medicine in Bladder Cancer

### 12.4.4.1 Tyrosine Kinase Receptors Inhibitors

#### Fibroblast Growth Factor Receptor (FGFR)-Targeted Therapies

Molecular studies have revealed meaningful molecular differences between NMIBC and MIBC [64] and identified several oncogenic targets available for the treatment of bladder cancer. The most representative of them is FGFR signaling [65]. FGFR signaling plays an important role in tumorigenesis. FGFR3 is known to be highly carcinogenic, and the activation of point mutations is common in low-grade, stage bladder cancer [64]. Low-grade papillary urothelial cancer and papillary urothelial neoplasms have mutations in over 80% of the low malignant potential [66]. In contrast, MIBC had few mutations and no mutations in CIS [65, 66]. Patients with FGFR3 mutations in Ta bladder tumors had a lower risk of recurrence and progression [67]. Patients with FGFR3 mutations in T1 tumors also had good prognosis [68]. Patients with FGFR3 mutations were also better in upper tract urothelial carcinoma. Targeting FGFR3 therapy can benefit most of the NMIBC and MIBC. The first phase I study, FGFR1, FGFR2, FGFR3, and FGFR4 inhibitor called JNJ-42756493 (clinicaltrials.gov identifier: NCT01703481), was evaluated. In a phase II trial, dovitinib, a small-molecule inhibiting FGFR1 and FGFR3 and VEGFR1, VEGFR12, and VEGFR13, has been tested in 44 patients with metastatic urothelial carcinoma with or without FGFR3 mutations [69]. However, this treatment resulted in no response in patients with FGFR3 mutations and an overall response rate of 3% in wild-type FGFR3 (clinicaltrials.gov identifier: NCT01732107).

### 12.4.4.2 Other RTK Inhibitors

#### Targeting PI3K/AKT/mTOR Pathway

In various cellular processes such as cell growth, cell survival, and cell metabolism, the phosphatidylinositol 3-kinase (PI3K/AKT/mTOR) signaling is an essential pathway. The PI3K/AKT/mTOR signaling pathway is altered in more than 40% of MIBC resulting either from activating mutations of PIK3CA (20%) or AKT1 (<5%) or inactivating deletions or mutations of PTEN (30%) or TSC1 (5–16%) [47]. Buparlisib (BKM120), an oral PI3K inhibitor, is currently ongoing in a phase II clinical trial in the second-line setting (clinicaltrials.gov identifier: NCT01551030). In addition, mTOR is a downstream target of PI3K/AKT/mTOR pathway that appears to play a central role in tumor growth. Rapamycin and everolimus, mTOR inhibitors, showed the efficacy in inhibiting the growth of bladder cancer cells in vitro [70].

#### Targeting EGFR

Although epidermal growth factor receptor (EGFR) was one of the first targets in urothelial cancer, epidermal growth factor receptor (EGFR) inhibitors have not reached their goal in the clinic [71]. Lapatinib, a bifunctional EGFR and HER-2 kinase inhibitor, was evaluated in a phase II/III in patients with EGFR and/or HER-2 overexpressing locally advanced or metastatic bladder cancer (clinicaltrials.gov identifier: NCT00949455). However, any clinical benefit of lapatinib compared to placebo in metastatic urothelial carcinoma was not reported [72].

#### 12.4.4.3 TCGA (The Cancer Genome Atlas)

Analysis of the molecular genetic characteristics of bladder cancer has been reported through The Cancer Genome Atlas (TCGA) [47]. Analysis of blood and cancer tissues in 131 patients with muscle-invasive bladder cancer revealed DNA alteration more frequently than other cancers. On average, 302 exon mutations, 204 genomic CNV, and 22 genomic rearrangements were found [47]. A large-scale analysis of the genetic and molecular characteristics of bladder cancer has been conducted before and after the TCGA study [47, 73–77]. Studies in major bladder carcinoma genomes have shown that they can be classified into several subtypes depending on their molecular characteristics [47, 73–77]. In particular, bladder cancer can be classified as luminal-type, basal-type, p53-like, and small cell carcinoma-like tumor, and the basal type has a poor prognosis than other subtypes [47, 73–77]. Basal-type and p53-like tumors are highly resistant to preoperative chemotherapy, and this is a very important factor in clinical decision-making [75]. In order to apply these molecular properties to clinical practice, a common consensus is required for various research results [78]. The researchers defined basal/squamous-like (BASQ) as a basal type of bladder cancer with a very poor prognosis and a high resistance to chemotherapy [78].

#### 12.4.4.4 COXEN (Co-expression Extrapolation)

It is a computer program that examines gene panels of patient tumors to predict response to chemotherapy. The US National Cancer Institute Developmental Therapeutics Program (NCI-DTP) has data on more than 40,000 compounds tested on various 60 human cancer cell line panels (NCI-60). The COXEN program is based on data known as NCI-60. The COXEN can predict drug susceptibility and effectiveness to tumors using gene expression profiles and tumor samples. The COXEN derives a biomarker by comparing gene expression dates between sensitive and resistant cell lines. Biomarkers are used to derive gene expression models and predict susceptibility and effectiveness for drugs [79]. In a COXEN study of the in vitro sensitivity of cisplatin and paclitaxel to bladder cancer, 85% of cisplatin and 78% of paclitaxel could accurately predict sensitivity and resistance to bladder cancer cell lines [80]. COXEN can be used to predict individual patient responding to specific chemotherapy in the future, and it may be helpful to assign patients with chemotherapy.

## 12.5 Chemotherapy for Nonurothelial Bladder Cancer

Nonurothelial bladder cancer accounts for between 5% and 10% of all bladder tumors [81]. Most genitourinary cancers are epithelial origin, including squamous cell carcinomas, adenocarcinomas, and small cell tumors. Nonepithelial cancers are unusual, and sarcoma, carcinosarcoma, paraganglioma, melanoma, and lymphoma are nonepithelial cancers. Information on the treatment of nonurothelial bladder cancer has not been well established yet but generally begins with an approach to patients with urothelial bladder cancer. Treatment options for metastatic nonurothelial bladder cancer were palliative care, radiation therapy, or chemotherapy. The prospective trial of ifosfamide, paclitaxel, and cisplatin in patients with advanced non-transitional cell carcinoma of the urothelial tract was reported [82]. Of 20 patients, 11 were adenocarcinoma, 8 were squamous cell carcinoma, and 1 was small cell carcinoma. [82]. The major response rate was 35%; median survival was 24.8 months [82].

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# Part III

# Upper Tract Urothelial Carcinoma

# Epidemiology and Pathophysiology

# 13

Bum Sik Tae and Chang Wook Jeong

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## 13.1 Epidemiology

### 13.1.1 Incidence and Gender

UTUC is relatively uncommon and comprises 5–10% of all urothelial tumors [1]. However, according to large contemporary series, the epidemiology of UTUC appeared to be largely influenced by its geographic distribution. In US and Western European countries, it is reported that UTUC to be approximately 1.5–2.5 times more prevalent in males than in females [1–6]. In addition, it is reported that tumor of renal pelvis is more common than in the ureter [3, 7, 8]. However, some series emerging from Asian regions such as Taiwan and Mainland China cite a much higher UTUC prevalence, accounting for up to 20–30% of all urothelial carcinomas in some areas [9, 10]. In these regions, UTUC is thought to be about 1.3 times more common among females than males with a relatively greater proportion of ureteral tumor [3, 10–12].

Study upon SEER database suggested that disease-specific annual mortality is greater in women than in men (6.1% vs. 4.4%) [13]. However, recent meta-analysis demonstrated that there is no significant association between gender

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and overall survival [14]. Whites are about twice as likely as African-Americans to develop UTUC [15]. On the other hand, SEER data suggest that disease-specific annual mortality is greater in black men than in white men (7.4% vs. 4.9%) [13]. The mean age at diagnosis is 65 years; however, UTUCs have a peak incidence in individuals aged 70–90 years [1]. In 17% of cases, concurrent urothelial cell carcinoma in bladder is present and recurrence in the bladder occurs in 22–47% of UTUC patients compared with 2–6% in the contralateral upper tract [1, 16].

## 13.1.2 Etiology

Etiology and natural history of upper urinary tract urothelial cell carcinoma is similar to that of urothelial cell carcinoma in bladder. As with UBC, smoking and exposure to certain industrial dyes or solvents are associated with an increased risk of UTUC [1]. Cigarette smoking appears to be the most important modifiable risk factors for UTUC, producing an incidence three times that seen in nonsmokers. According to recent reports, tobacco exposure increases the relative risk from 2.5 to 7 [1]. In addition, excess inorganic arsenic in drinking water from artesian wells is a major health hazard in certain parts of the world and is associated with an increased risk of UTUC in addition to other diseases [17].

### 13.1.2.1 Analgesics

Long time and large quantities of analgesic combinations containing acetaminophen and phenacetin consumption is associated with an increased risk of urothelial cell carcinoma of the renal pelvis and bladder, especially in middle-aged women [18, 19]. In one study, 22% of patients with renal pelvic tumors and 11% of patients with ureteral tumors reported a history of analgesic abuse with a latency period of approximately 2 years [20]. Histologic findings associated with analgesic abuse include thickening of the basement membrane (pathognomonic) and papillary scarring [21]. The degree of papillary scarring also appears to be closely related to tumor grade, although not with the development of squamous metaplasia or squamous cancer [22].

### 13.1.2.2 Balkan Nephropathy

Balkan nephropathy is characterized by a degenerative interstitial nephropathy occurring in Yugoslavians, Rumanians, Bulgarians, and Greeks. Balkan nephropathy associated with UTUC is generally superficial and more likely to be bilateral [21]. The aristolochic acid is associated with a specific mutation in the p53 gene at codon 139 that occurs mainly in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy who present with UTUC [1, 17, 23]. Although the incidence of Balkan endemic nephropathy is also declining, aristolochic acid plays a key role in the pathophysiology of this nephropathy [1].

### 13.1.2.3 Arsenic

Chronic exposure to arsenic in southwestern Taiwan has long been associated with a form of peripheral vascular disease known as blackfoot disease that causes dry gangrene of the extremities. Throughout all regions of Taiwan an increased rate of UTUC has been noted. These tumors behave in a similar fashion to other UTUCs of similar grade and stage.

### 13.1.2.4 Smoking and Coffee

Smoking is known to be the most important risk factors for UTUC, producing an incidence three times that seen in nonsmokers [21]. Risk from smoking seems more often to lead to ureteral rather than to renal pelvic tumors. Otherwise, Ross et al. reported that a relative risk of 1.8 times normal has been described in individuals who consumed more than seven cups of coffee per day [24]. However, after adjustment of smoking, this risk decreased to 1.3.

### 13.1.2.5 Chronic Inflammation, Infection, or Exposure to Chemotherapeutic Agents

Lynch syndrome II is characterized by the early development of colonic tumors (without polyposis) and extracolonic neoplasms, including UTUC. Unlike with nonhereditary cancers, these patients are typically younger (mean, 55 years) and are more likely to be female. In addition, exposure to cyclophosphamide, an alkylating agent, also appears to confer an increased risk [25].

#### 13.1.2.6 Occupation

Persons employed in chemical, petroleum, plastic industries have relatively high risk of UTUC. And history of exposure to coal, coke, asphalt, or tar is also associated with developing UTUC [21]. Aniline dyes, β-naphthylamine, and benzidine have been implicated as causative agents, and tumors can occur at long intervals (up to 15 years or more) after exposure.

### 13.1.3 Natural History and Mortality

Ureteral tumors occur more commonly in the lower than in the upper ureter. Overall, about 70% of ureteral tumors occur in the distal ureter, 25% in the mid-ureter, and 5% in the proximal ureter [21]. Bilateral involvement (either synchronous or metachronous) occurs in 1.6–6.0% of sporadic UTUC. Patients with a single upper tract carcinoma are at risk of developing bladder cancer (30–50%) [21]. Conversely, patients with primary bladder cancer are at low risk (<2%) of developing upper urinary tract cancers. However, patients with multiple recurrent superficial and in situ bladder cancers that are successfully treated by transurethral resection and BCG are at a substantial lifelong risk of developing UTUC [26].

UTUCs are often associated with a poor prognosis. Up to 19% of patients with UTUC have been reported to present initially with metastatic disease. One multicenter study reported that although upper tract urothelial cancers were more often invasive and more often poorly differentiated than bladder cancers, in pathologically matched cohorts recurrence with less aggressive disease, progression to more advanced disease, and death occurred with equal frequency among patients with upper tract and lower tract (bladder) urothelial cancers. Among them, renal pelvis tumors have a better overall prognosis and 5-year recurrence-free and cancer-specific survivals than do ureteral tumors. However, overall prognosis of UTUC seems to be principally related to tumor stage and to a lesser degree to tumor grade.

Because renal pelvis and ureter have relatively this muscle layer, invasive upper tract tumors can penetrate earlier than is seen in bladder cancers. High-grade and deeply invasive urothelial cell carcinoma occurred in 28.2% of bladder cancers compared with 39.5% of UTUC. The renal parenchyma itself may be a barrier to the spread of stage T3 cancers, whereas periureteral tumor extension is a risk factor for early tumor dissemination [21].

UTUC may spread in several different ways, including direct invasion into the renal parenchyma or surrounding structures, lymphatic or vascular invasion, and epithelial spread by seeding or direct extension. Especially, high-grade tumors have a greater propensity to invade and that renal parenchymal invasion is the most significant predictor of the development of metastases (95%), followed by vascular invasion (83%) and lymphatic invasion (77%). Lymphatic spread from the upper urinary tract extends to the para-aortic, paracaval, and ipsilateral common iliac and pelvic lymph nodes [28]. Lymphatic invasion depends on the location of the primary tumor and is directly related to the depth of invasion of the primary tumor. Otherwise, the most common sites of hematogenous metastases from upper tract tumors are the liver, lung, and bone.

## 13.2 Pathology

The mucosal lining of the renal pelvis and ureter is similar to that of the urinary bladder, being composed of transitional cell epithelium. Therefore, most renal pelvic and ureteral cancers (90% and 97%, respectively) are transitional cell carcinoma (TCC). However, the urothelial lining of the upper urinary tract markedly reduced the thickness of the muscle layer and the abutting of the urothelium onto the renal parenchyma proximally. The epithelial layer is continuous from the level of the calyces to the distal ureter.

### 13.2.1 Metaplasia, Dysplasia, and Benign Lesion

Several studies have suggested that upper tract urothelial cancers progress through histologic changes from hyperplasia to dysplasia to frank carcinoma in situ in a significant proportion of patients [21]. Otherwise, inverted papillomas, although generally considered benign lesions, often have been shown to be associated with either synchronous or metachronous UTUC [21]. However, 18% incidence of malignancy is associated with inverted papilloma of the ureter.

### 13.2.2 Transitional Cell Carcinoma

As mentioned above, TCC makes up more than 90% of UTUCs, may present as papillary or sessile lesions, and may be unifocal or multifocal [21]. The histologic characteristics and biology of UTUC are very important factors that affect treatment decisions. Approximately 85% of renal pelvis tumors are papillary; the remainder are sessile [21]. However, the stage of upper tract tumors is T1 or T2 in approximately 50% of papillary and 80% of sessile lesions, respectively. Thus, 50–60% of renal pelvis tumors are invasive, in contrast to most bladder tumors, which are noninvasive; 55–75% of ureteral tumors are low grade and low stage, but invasion is still more common than among bladder tumors [21].

### 13.2.3 Unusual Variant Histology

Variant histology(VH) in UBC is generally an unfavorable prognostic factor in association with high-grade and advanced pathologic stage at the time of presentation [26]. In addition, several studies reported that VH in UTUC is associated with poor prognosis [27, 28]. Therefore, some researchers reported that some patients with VH were needed to receive adjuvant chemotherapy and intensive surveillance protocols [28–30]. A large number of morphological variants of urothelial carcinomas of the upper urinary tract have been described.

#### 13.2.3.1 Micropapillary Carcinoma

The micropapillary variant of urothelial carcinoma (MPUC) is a rare form of urothelial carcinoma that accounted for 2.6% of all UTUCs [31]. The invasive pattern of micropapillary carcinoma consists of small clusters of neoplastic epithelial cells with high nuclear grade that form tight, small micropapillary structures surrounded by a clear retraction artifact.

#### 13.2.3.2 Lymphoepithelioma-Like Carcinoma

Tumors with similar morphological features have been designated as lymphoepithelioma-like carcinoma (LELC) and have been reported in several organs such as the salivary glands, lung, thymus, cervix, skin, stomach, bladder, and renal pelvis. LELC in renal pelvis is known that the Epstein-Barr virus genome was negative in situ hybridization study [32]. The histology of LELC is characterized by islands of cells with large, vesicular nuclei with prominent eosinophilic nucleoli, parachromatin clearing and high mitotic activity [33]. The cytoplasm of the tumor cells is amphophilic with ill-defined cell borders, giving the tumor a syncytial appearance [33].

#### 13.2.3.3 Sarcomatoid Carcinoma

Sarcomatoid variant is another rare type of variant form and several studies reported that it is strongly associated with poor prognosis of UTUC patients [33, 34]. It is characterized by a proliferation of atypical spindle cells arranged in short interlacing fascicles or showing a vague storiform pattern [35]. Perez-Montiel demonstrated that the nuclei of sarcomatoid variant show coarsely clumped chromatin and prominent, often multiple, nucleoli, and are surrounded by scant, lightly eosinophilic cytoplasm [35]. Areas of transition with conventional urothelial carcinoma can generally be identified. The differential diagnosis for these lesions includes a variety of spindle cell sarcomas, both primary and secondary, and secondary infiltration of the renal pelvis by sarcomatoid renal cell carcinoma. In addition, presence of a prominent pseudosarcomatous myofibroblastic reaction in the stroma of a urothelial carcinoma of the upper urinary tract should also be differentiated.

#### 13.2.3.4 Squamous Cell Carcinoma and Urothelial Carcinoma with Squamous Differentiation

Squamous cell cancers (SCCs) make up 0.7–7.0% of UTUC; however, it has been reported in the renal pelvis and accounts for 10% of cases in some series [21, 36]. Stewart et al. reported that SCCs are frequently associated with a condition of chronic inflammation or infection or with analgesic abuse [21]. SCCs occur six times more frequently in the renal pelvis than in the ureter and are generally moderately to poorly differentiated and more likely to be invasive at the time of presentation [21]. Tumors with foci of squamous differentiation in the renal pelvis are about 12% of all high-grade urothelial carcinomas in some retrospective studies [33]. Moreover, SCCs are usually associated with calculi, chronic infection, and squamous metaplasia of the neighboring epithelium [36, 37]. Although most of keratinizing tumors associated with high nuclear grade and had poor prognosis, but there is one case report of verrucous carcinoma associated with urolithiasis that had good clinical outcome [38]. Foci of squamous differentiation within otherwise conventional UTUC, however, are more frequent than the development of pure squamous cell carcinoma. The tumors are histologically characterized by prominent areas of squamous differentiation, sometimes displaying basaloid or clear cell features [35]. It is recommended that tumors with basaloid or clear cell features should be reported as urothelial carcinomas with squamous differentiation and that an estimate of the percentage squamous component be included in the report.

#### 13.2.3.5 Clear Cell

Clear cell change is characterized by nests or sheets of cells containing abundant clear cytoplasm with well-defined cell membranes and it is observed in 20–40% of high-grade urothelial carcinomas [33]. In the bladder, it should be differentiated from adenocarcinomas of Müllerian origin, or from metastases of a clear cell renal cell carcinoma (RCC) [39]. Otherwise, in renal pelvis, the main differential diagnosis is with secondary invasion by a clear cell RCC. Immunohistochemical stains can help in distinguishing clear cell RCC from high-grade UTUC.

#### 13.2.3.6 Adenocarcinoma and Urothelial Carcinomas with Glandular Differentiation

These variant types have been associated with stones, intestinal metaplasia, and long-standing hydronephrosis, however, it is extremely rare and accounts for below 1% of all tumors in this location [35]. However, it also typically presents at advanced stage and displays a poor prognosis [21]. Mucinous adenocarcinomas are the most frequent histological type. The adenocarcinomatous areas are characterized by well-formed glands lined by atypical cells with large nuclei and moderate amounts of mucinous cytoplasm [35].

#### 13.2.3.7 Plasmacytoid Cells

Urothelial carcinoma with plasmacytoid features is a rare variant of urothelial neoplasm described in the urinary bladder in association with high-grade tumors, and is generally associated with poor survival outcome [40]. Histologically, the tumor cells have eccentric nuclei and are surrounded by an ample rim of abundant, deeply eosinophilic cytoplasm, imparting the cell with a striking plasmacytoid appearance. However, plasmacytoid lymphoma and a plasmacytoma should be distinguished from plasmacytoid in UTUC.

#### 13.2.3.8 Small Cell Carcinoma

In bladder, small cell carcinoma has been reported predominantly affecting older patients and associated with a poor prognosis. However, in UTUC, only a few case reports have been published and all of them have been combined with urothelial carcinoma or, less frequently, with squamous cell carcinoma [41]. Histologically, small cell carcinoma variant in UTUC is similar to their pulmonary counterpart with small, uniform cells with nuclear molding, scant cytoplasm, and nuclei containing finely dispersed chromatin with small or inconspicuous nucleoli [42].

#### 13.2.3.9 Tumors with Rhabdoid Features

Features of "rhabdoid" tumor in UTUC have been observed in high-grade tumor and the tumor cells have abundant cytoplasm with paranuclear eosinophilic inclusions corresponding to whorls of intermediate filaments as seen by electron microscopy [35]. Epithelial tumor giant cells, which are associated with high-grade urothelial carcinoma, or tumors characterized by a prominent component of foreign body type or osteoclastic giant cells should be distinguished from UTUC with rhabdoid features.

## 13.3 Staging

The Tumor-Node-Metastasis (TNM) staging system has been recognized globally for decades as the standard in staging cancers for cancer classification, prognostication, treatment, data registry, and clinical trials and research [43, 44]. The updates and emphasis in the 8th edition of the AJCC Cancer Staging Manual (8E AJCC) classification are most evident in the pathological aspects of staging and other prognostic factors [43]. However, there are no data to substantiate the three N categories in the 7th AJCC edition, the previous category of N3 metastasis in a LN greater than 5 cm is now collapsed with N2 in 8E AJCC (level of evidence III). Moreover, there is no significant update in 8E AJCC in UTUC compared with 7th AJCC edition.

The TNM classification in UTUC is shown in Table 13.1. The regional lymph nodes are the hilar and retroperitoneal nodes, and for the mid and distal ureter, the intra-pelvic nodes. Laterality does not affect N classification [1]. The classification and morphology of UTUC and bladder carcinoma are similar [1]. Renal pelvic pT3 subclassification may discriminate between microscopic infiltration of the renal parenchyma (pT3a) and macroscopic infiltration or invasion of peripelvic adipose tissue (pT3b). Staging errors exist when one compares the clinical stage (based on physical examination and imaging) with the pathologic stage (based on removal of the bladder and regional lymph nodes). Overstaging is relatively uncommon, but clinical understaging may occur in up to 53% of patients.

**Table 13.1** TNM classification 2017 for upper urinary tract urothelial carcinoma

| T—primary tumor | |
|---|---|
| Tx | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Ta | Noninvasive papillary carcinoma |
| Tis | Carcinoma in situ |
| T1 | Tumor invades subepithelial connective tissue |
| T2 | Tumor invades muscularis |
| T3 | Tumor invades beyond muscularis into peripelvic fat or renal parenchyma (renal pelvis)<br>Tumor invades beyond muscularis into periureteric fat (ureter) |
| T4 | Tumor invades adjacent organs or through the kidney into perinephric fat |
| N—regional lymph node | |
| Nx | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in a single lymph node ≤2 cm in the greatest dimension |
| N2 | Metastasis in a single lymph node >2 cm, or multiple lymph nodes |
| M—distant metastasis | |
| Mx | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

Source: Adapted from Gospodarowicz MK, Brierley JD, Wittekind C. TNM classification of malignant tumours. John Wiley & Sons; 2017. Permitted by John Wiley and Sons

Until 2004, the 1973 World Health Organization (WHO) classification was used for tumor grading and distinguishing grades G1–G3. The 2004 WHO classification considers histological data to distinguish between noninvasive tumors: papillary urothelial neoplasia of low malignant potential, and low- and high-grade carcinomas (low grade versus high grade). The current guidelines are based on the 2004 WHO classifications [45].

It is possible to distinguish between noninvasive papillary tumors (papillary urothelial tumors of low malignant potential and low- and high-grade papillary UC), flat lesions (carcinoma in situ [CIS]), and invasive carcinoma [1]. There is a strong correlation between grade and stage for upper tract tumors. The single most important determinant of outcome is tumor stage [21].

pNx is used when lymph nodes cannot be assessed. When no lymph nodes are examined, pNx should be assigned. pN0 means no lymph node metastasis. pN1 means metastasis in a single lymph node ≤2 cm in the greatest dimension and pN2 represents single lymph node over 2 cm and multiple regional lymph node metastases.

If distant metastasis is present, M category is designated as M1. UTUC spread in the same way as bladder tumors do, through lymphatic and hematogenous routes and by direct extension into contiguous structures. Therefore, the common metastatic of UTUC sites include the lungs, liver, and bones [21]. So preoperative evaluation for the extent of disease includes chest radiography, abdominal CT, liver function tests, and occasional bone scintigraphy.

Since renal pelvis and ureter have thin muscle layer, invasive UTUC can penetrate muscle layer than that of bladder. However, this is not a valid reason for radical versus conservative treatment if a lesion is either noninvasive or invasive and organ confined (stage T2). Moreover, the renal parenchyma may be a barrier, slowing distant spread of stage T3 renal pelvis tumors. In contrast, periureteral tumor extension carries a high risk of early tumor dissemination along the periureteral vascular and lymphatic supply.

## 13.4 UTUC After Known Bladder Cancer

According to SEER database, UTUCs developed in 657 of 91,245 cases of bladder cancer with adequate follow-up (median 4.1 years) from 1973 to 1996 [21]. The relative risk for UTUC for white men and women was 64.2% and 75.4% at or before 2 years, 44.3% and 40.5% at 2–5 years, 50.8% and 42.1% at 5–10 years, and 43.2% and 22.2% at more than 10 years, respectively [21]. The incidence of upper tract recurrence has been shown to be higher in patients with CIS than in patients with noninvasive papillary tumor and in patients treated with cystectomy for CIS rather than for invasive cancer [46].

The risk of upper urinary tract recurrence after radical cystectomy is approximately 3–6% and tumor grade, stage, multifocality, and the presence of bladder or prostatic carcinoma-in situ (CIS) are risk factors for recurrence in upper urinary tract [47]. Volkmer et al. reported that 1.8% (25/1420) had upper tract recurrence in their retrospective study. In addition, they quoted eight reports that included relatively high numbers of patients, and showed that 3.2% (205/6381) patients had upper tract recurrence [47]. In SEER database study, recurrence in upper urinary tract is also more likely to occur with high-grade UBC (hazard ratio [HR] 2.16), in T1 versus Ta disease (HR 1.16), and in patients with trigonal or periureteral presentation (HR 1.76) in multivariate analysis [48].

Most of these recurrences are only found in an advanced or metastatic disease, which is reflected in the poor survival outcome [47]. In a large multicenter study, of these patients 70–80% will die of progressing upper urinary tract recurrence. Therefore, patients who underwent radical cystectomy with symptoms like hematuria or hydronephrosis would initiate immediate further examinations [47]. Retrograde urography and flexible ureteroscopy are valuable examination tools for upper tract recurrence when the bladder is still intact. However, in patients with urinary diversion the site of ureteral implantation to the reservoir is not detectable or accessible and, thus, requires a much more invasive percutaneous or even open access procedure to clarify the situation, with much higher rates of false-positive findings in the cystectomy patients [47]. Regular follow-up examinations with radiation exposure have a poor detection rate in patients without any risk factors for upper tract recurrence (0.8% in 15 years). In these patients, urinalysis, urine cytology, and ultrasound examinations might be sufficient to guarantee a safe follow-up regimen. These examinations are recommended to prevent complications such as obstructive upper tract uropathy or uremia [47].

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# Diagnosis and Prognostic Factors of UTUC

# 14

Bum Sik Tae and Chang Wook Jeong

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## 14.1 Symptom and Sign

Most common symptom of UTUC is hematuria, either gross or microscopic (70–80%) [1]. Flank pain is the second most common symptom, occurring in 20% of tumors, and a lumbar mass is present in approximately 10% [1]. Current pain is the result of ureteral obstruction from blood clots or tumor fragments, renal pelvic or ureteral obstruction by the tumor itself, or regional invasion by the tumor. It is known that flank pain in patients does not correlate with either locally advanced tumor

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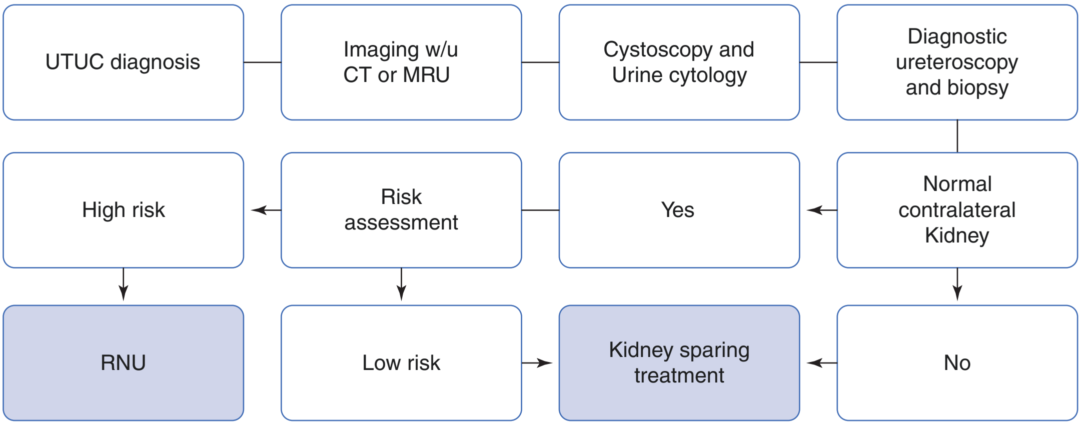

| Risk Assessment | | |
|---|---|---|
| | Low Risk | High Risk |
| Biopsy finding | Low grade | High grade |
| Urine cytology | Negative | Positive |
| Tumor size | <1cm | <1cm |
| Multifocality | No | Yes |
| Hydronephrosis | No | Yes |
| Imaging sign | No invasive sign | Invasive sign |

**Fig. 14.1** Risk stratification of upper urinary tract urothelial carcinoma. *UTUC* upper urinary tract urothelial carcinoma, *CT* computed tomography, *MRU* magnetic resonance urography

stage or worse prognosis, as is the case with bladder cancer [2]. In addition, irritative voiding symptoms are also present in approximately 5–10% of patients [3]. Systemic symptoms (including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) associated with UTUC should prompt more rigorous metastatic evaluation; they confer a worse prognosis [1]. Supraclavicular or inguinal adenopathy or hepatomegaly may be founded in a small percentage of patients with metastatic disease. However, about 15% of patients are asymptomatic at presentation and are diagnosed when an incidental lesion is found on radiologic evaluation (e.g., computed tomography) (Fig. 14.1).

## 14.2 Laboratory Finding

### 14.2.1 Urinalysis

As mentioned above, hematuria is identified in most patients with UTUC but may be intermittent. The diagnostic role of urinalysis in UTUC is similar in urothelial cell carcinoma in the bladder, presented in previous NMIBC Chapters. Dipstick urinalysis is a simple and useful diagnostic tool; however, there is consensus among the North American guidelines that urine dipstick alone is inadequate to establish a diagnosis of microscopic hematuria [4]. Therefore, guidelines suggest that if a dipstick is positive for hematuria, results should be confirmed by performing a urinalysis with microscopic evaluation of the urinary sediment of a freshly voided, clean-catch, midstream urine sample. In the event of a positive urine dipstick and negative urinalysis with microscopy, the American Urologic Association (AUA) recommends that urinalysis with microscopy should be repeated three times, with full evaluation if any are positive [4]. Both the AUA and American College of Physicians (ACP) define AMH as the presence of ≥3 red blood cells (RBCs) per high-power field in a single properly collected specimen [4, 5]. On the other hand, none of the European guidelines comment on the degree of hematuria on urine microscopy. In addition, pyuria and bacteriuria may be identified in patients with concomitant urinary tract infection from obstruction and urinary stasis [6].

### 14.2.2 Urine Cytology

Urine cytology is a specific tool that is useful in the diagnosis of upper tract carcinomas [7]. The role of urine cytology includes detecting lesions that are not seen by imaging or not visually recognized during cystoscopy or ureterorenoscopy.

Positive urine cytology is suggestive of UTUC when bladder cystoscopy is normal, provided no carcinoma in situ in the bladder or prostatic urethra has been detected [1]. Overall accuracy estimates of the sensitivity of cytology have ranged from about 20% for grade 1 tumors to 45% and 75% for high-grade tumor [8]. Various studies demonstrated that positive cytology results are correlated with high-grade and non-organ-confined UTUC. In a multi-institutional cohort, 80% of 172 patients had positive cytology findings, and positive urine cytology was independently associated with non-organ-confined disease in multivariate analysis (HR 3.1, $p = 0.035$) [9]. Recently, Messer et al. reported that inclusion of atypical cytology with positive cytology improved the sensitivity and positive predictive value for high-grade (74% and 63%) and muscle-invasive (77% and 45%) UTUC [7].

However, urine cytology is less sensitive for UTUC than bladder cancers and should be performed in situ in the renal cavities. According to the EAU guideline, urine cytology is also included in the recommended diagnostic workup for UTUC, but its value in this process is poorly defined [1]. To improve accuracy of diagnosis, urine cytology can be performed in selective urine through catheterization, washing, or brushing the cavities and lumen of the suspected renoureteral unit. EAU guideline recommended that urinary cytology of the renal cavities and ureteral lumina is preferred before application of a contrast agent for retrograde ureteropyelography because it may cause deterioration of cytological specimens [1, 10].

### 14.2.3 Urinary Markers

Urine-based test that uses spontaneously voided urine and provides diagnostic information with high sensitivity and specificity would be ideal. To overcome limited accuracy of urine cytology in UTUC, many investigators have evaluated the role of molecular urine-based tests.

#### 14.2.3.1 Cytogenetic Test for Chromosomal Aberrations

Fluorescence in situ hybridization (FISH) is one of the useful assays used. The sensitivity of fluorescence in situ hybridization (FISH) for molecular abnormalities characteristic of UTUCs parallels its performance in bladder cancer [1]. Early results suggest that FISH also may be useful in the diagnosis of upper tract urothelial tumors. Luo et al. presented that overall sensitivity of FISH (for chromosomes 3, 7, 17 and the CDKN2A (9p21) gene) was significantly higher than that of cytology, while specificity for both was 100% [11]. However, its use may be limited by the preponderance of low-grade recurrent disease in the population undergoing surveillance and kidney-sparing therapy for UTUCs [1]. EAU guideline presented that FISH has limited value in the surveillance of UTUCs [1].

#### 14.2.3.2 Immunocytochemical Test for Tumor-Specific Antigens

uCyt + (ImmunoCyt) is an immunocytochemical test based on three monoclonal antibodies that are directed against antigens expressed on urothelial carcinomas (M344, LDQ10, and 19A211) [12]. In recent meta-analysis, average sensitivity and specificity values of ImmunoCyt were 78% (68–85%) and 78% (72–82%) in 1,042 patients [13]. In comparison with urine cytology, ImmunoCyt had a higher sensitivity (34–35% versus 67–86%) and slightly lower specificity (94–99% versus 75–79%) across all types of urothelial tumors [14]. However, no clear differences between the tests in sensitivity values for tumor stage Ta or T1 or low-grade bladder cancer were found [13].

## 14.3 Imaging

### 14.3.1 Computed Tomography

CT is easier to perform and less labor intensive than intravenous urography. It also has a higher degree of accuracy in determining the presence of renal parenchymal lesions. EAU guideline recommends that CT urography has the highest diagnostic accuracy of the available imaging techniques [1]. Therefore, hematuria work-up includes CT urography to assess for UTUC, a practice that maintains a strong recommendation (grade A) from EAU [1]. It is known that the sensitivity of CT urography for UTUC is 0.67–1.0 and specificity is 0.93–0.99 [1]. In SEER data, usage of CT urography increased the most, going from 2% in 1992 to 44% in 2009 [15]. Radiolucent filling defects, obstruction or incomplete filling of a part of the upper tract, and non-visualization of the collecting system are the typical findings suggestive of an UTUC.

Blood clot, stones, overlying bowel gas, external compression, sloughed papilla, and fungus ball should be distinguished from diseases that can cause filling defects. The impact of non-visualization for renal pelvis tumors versus ureteral tumors as indicators of a higher stage is uncertain (Fig. 14.2) [16]. However, hydronephrosis is associated with advanced disease and poor oncological outcome [1, 17]. In addition, the presence of enlarged lymph nodes in CT is highly predictive of metastases in UTUC (Fig. 14.3) [1]. CT predicted TNM stage in 60% of patients; it understaged 16% and overstaged 24% [18].

### 14.3.2 Magnetic Resonance Urography

Magnetic resonance (MR) urography is indicated in patients who cannot undergo CT urography, usually when radiation or iodinated contrast media are contraindicated [1]. The sensitivity of MR urography is 0.75 after contrast injection for small tumor (below 2 cm) (Fig. 14.4) [1]. In SEER data, usage of MR urography is just 6% in UTUC patients [15]. The use of MR urography with gadolinium-based contrast media has risk of nephrogenic systemic fibrosis. Therefore, it should be limited in patients with chronic kidney disease (CKD) stage 4 and 5 (<30 ml/min creatinine clearance) [1]. CT urography is generally preferred to MR urography for diagnosing and staging UTUC [1].

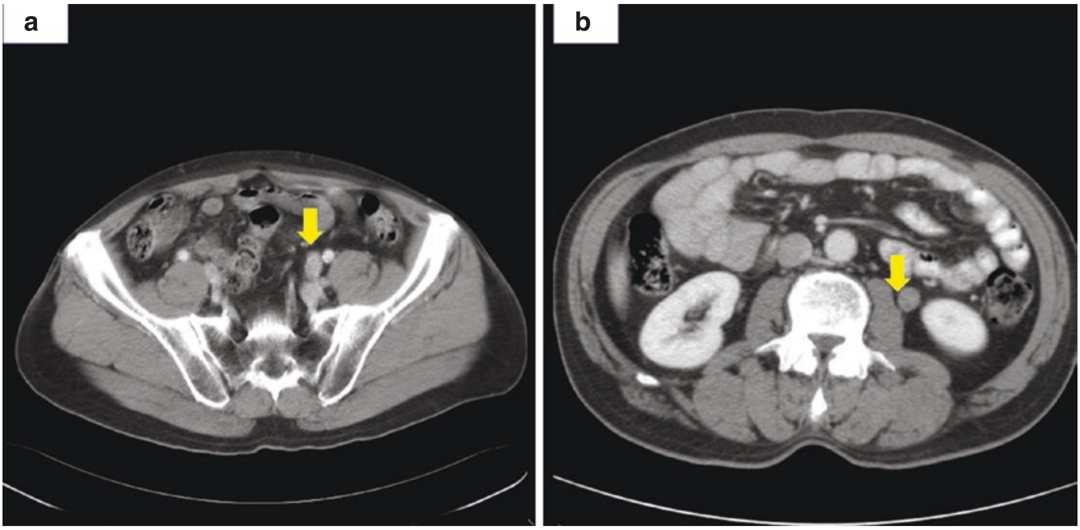

**Fig. 14.2** Upper urinary tract urothelial carcinoma finding in computed tomography. (**a**) Finding of distal ureter tumor (final pathology: T1), (**b**) finding of upper ureter tumor (final pathology: T1)

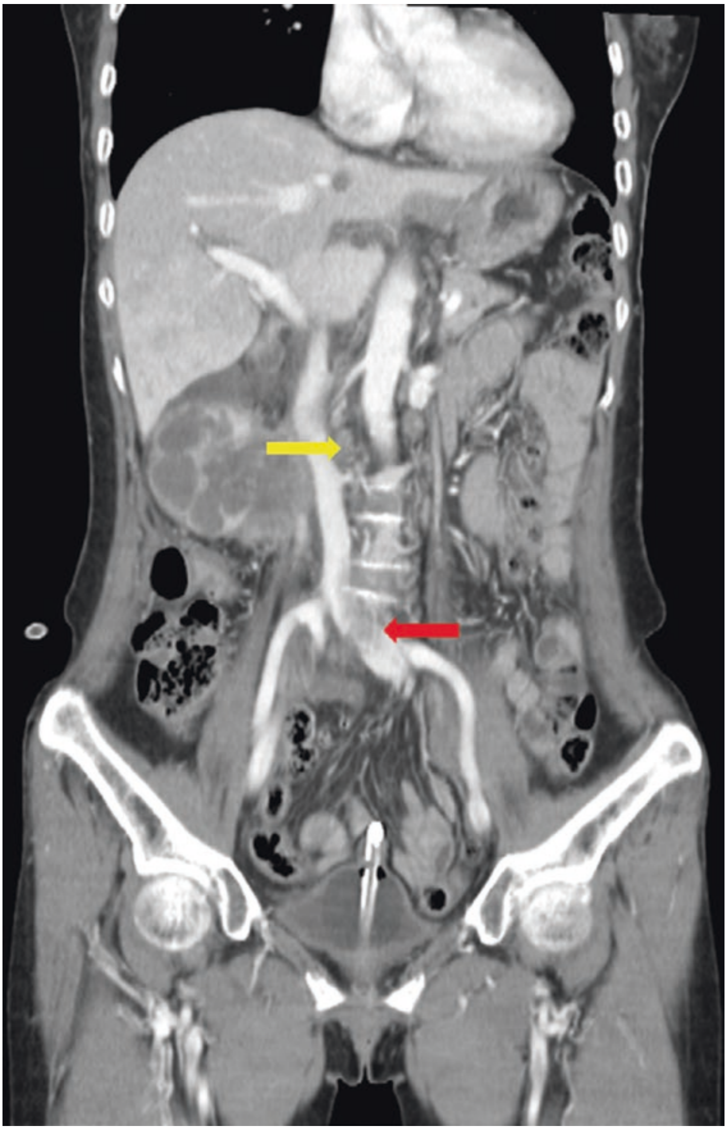

**Fig. 14.3** Finding of advanced upper urinary tract carcinoma (final pathology: T4 N2) in computed tomography. Yellow arrow indicates that invasion in hilar and para-aortic lymph nodes. Red arrow indicates tumor thrombus in IVC (rare finding)

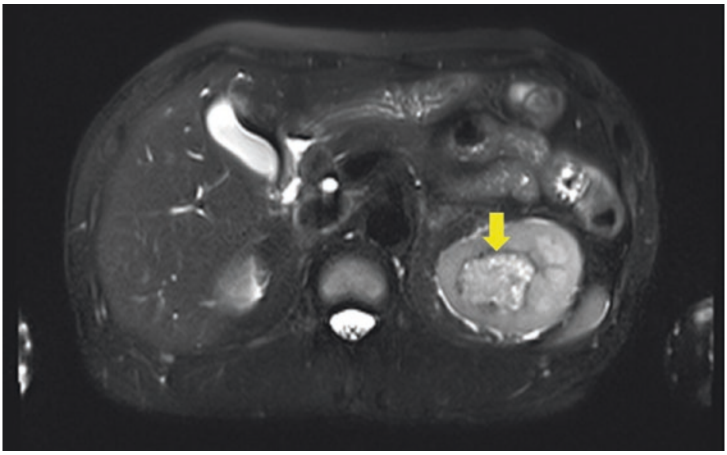

**Fig. 14.4** Upper urinary tract urothelial carcinoma finding in magnetic resonance urography (T2-weighted imaging)

### 14.3.3 Anterograde Pyelography, Retrograde Pyelography, and Sonography

Some have suggested that ultrasonography has sensitivity equal to that of urography in evaluating patients with painless gross hematuria for upper tract malignant disease. This is mainly due to its ability to detect renal masses and hydronephrosis. However, for staging purposes, ultrasonography is not suitable in determining the extent of invasion, an associated mass lesion outside the collecting system, and the presence of lymph node or distant metastases [18].

UTUC has historically been detected using intravenous urography (IVU) and retrograde pyelography (RGP) (Fig. 14.5). Today, cross-sectional imaging modalities, such as MR urography and CT urography, allow urologists to visualize the upper tract and potentially the invasiveness of a tumor into surrounding tissues [15]. Reported sensitivities of IVU and RGP for detecting UTUC are 37.5–85% and 25–100%, respectively [19–22]. During RGP, contrast material is injected into the ureteral orifice with a bulb or acorn-tip catheter. Intraluminal filling defects may then be identified in the ureter or renal pelvis. Ureteral tumors are often characterized by dilation of the ureter distal to the lesion, creating the appearance of a “goblet.” Nonopaque ureteral calculi appear as a narrowing of the ureter distal to the calculus. A ureteral catheter passed up the ureter may coil distal to a ureteral tumor (Bergman’s sign) [23].

### 14.3.4 Bone Scintigraphy

UTUCs spread in the same ways as bladder cancers do, through lymphatic and hematogenous routes and by direct extension into contiguous structures. In urothelial cell carcinoma, bone metastases were mostly in the pelvis or lower spine and were asymptomatic in 19% of patients (Fig. 14.6). In addition, the predominant metastatic sites are the lungs, liver, bones, and regional lymph nodes [24]. Preoperative evaluation for the extent of disease includes chest radiography, abdominal CT, liver function tests, and occasional bone scintigraphy [18]. In large retrospec-

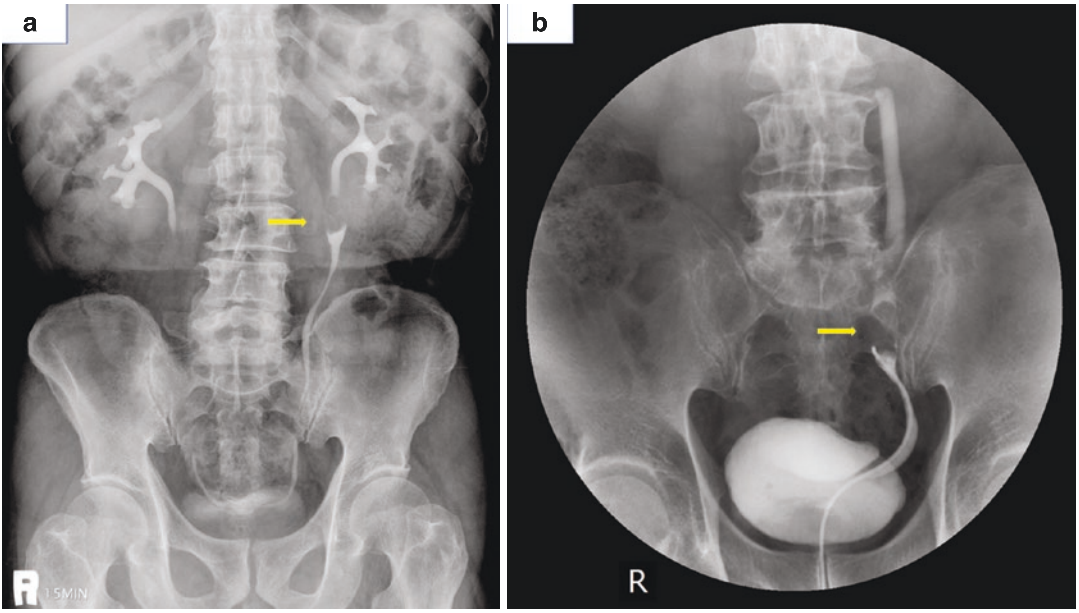

**Fig. 14.5** Upper urinary tract urothelial carcinoma finding in intravenous urography (IVU) (**a**) and retrograde pyelography (RGP) (**b**). Filling defects (yellow arrow) indicate suspicious ureter tumor lesions (goblet sign)

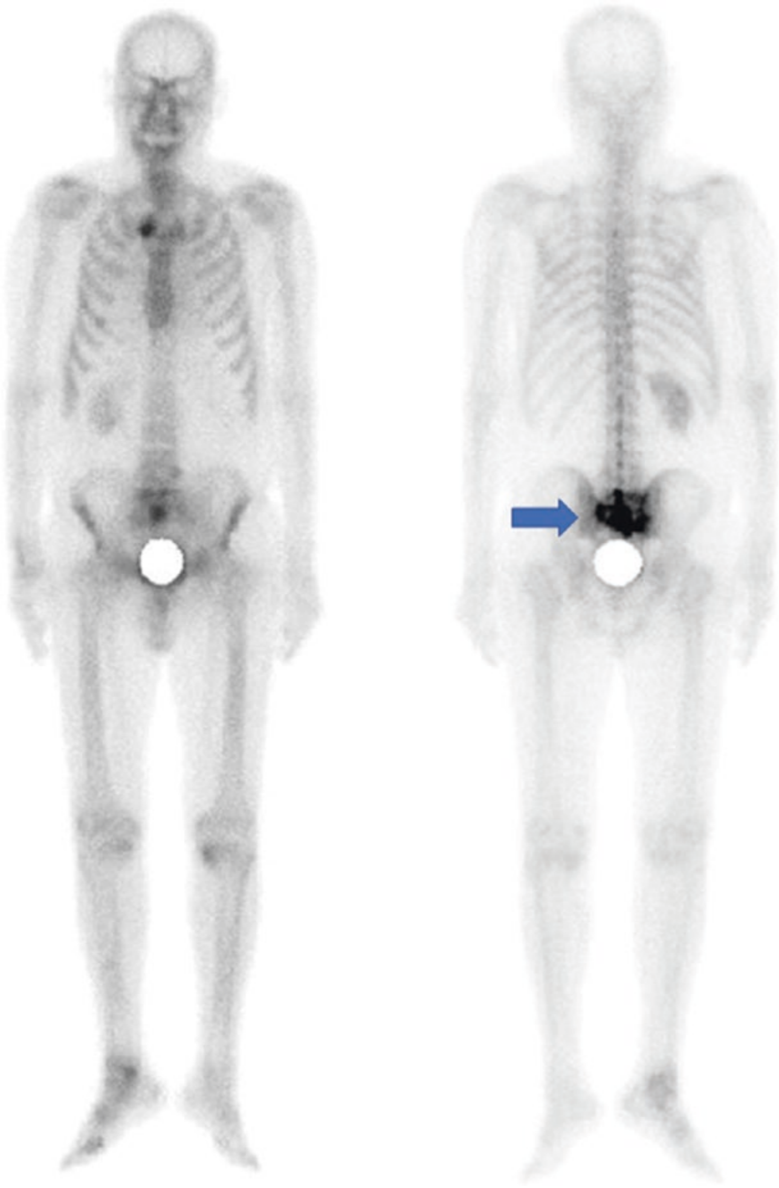

**Fig. 14.6** Image of bone scintigraphy in metastatic upper urinary tract urothelial carcinoma. Suspicious bone metastatic lesion in sacrum was seen (blue arrow)

tive multi-institutional cohort study, cumulative incidence rates of first disease recurrence after radical surgery at 1 and 3 years were 18.9 and 29.8% [24]. Of them, cumulative incidence rates of bone recurrence after radical surgery at 1 and 3 years were 3.3 and 4.9%. Especially, over pathologic T3 stage and lymph node metastasis is correlated with recurrence in bone after radical surgery [24].

## 14.4 Endoscopic Evaluation

### 14.4.1 Cystoscopy

The technique, indication, and practice of cystoscopy are presented in NMIBC Chapters. Because UTUC are often associated with bladder cancers, cystoscopy is mandatory in the evaluation to exclude coexistent bladder lesions [18]. As mentioned above concurrent urothelial cell carcinoma in the bladder is present in 17% of UTUC patients [1]. In addition, 22–47% of UTUC patients showed recurrence in the bladder. In addition, even if there is no bladder lesion in the cystoscopy, it is very important to confirm the blood jetting of the ureteral orifice. If there is no specific lesion in the bladder with non-specific finding in radiologic examinations such as CT, RGP or ureteroscopy is required if blood jetting is identified.

### 14.4.2 Ureteroscopy and Biopsy

The use of rigid and flexible ureteroscopy has allowed direct visualization of upper urinary tract tumors. Diagnostic accuracy can be improved from approximately 75% with excretory or retrograde urography alone to 85–90% when it is combined with ureteroscopy (Fig. 14.7) [25]. Ureteroscopic biopsies can determine tumor grade in 90% of cases with a low false-negative rate, regardless of sample size. Because of the small size of ureteroscopic biopsy specimens, a precise correlation with eventual tumor stage is difficult. Therefore, in predicting the tumor stage, a combination of the radiographic studies, the visualized appearance of the tumor, and the tumor grade provides the surgeon with the best estimation of eventual tumor stage [18].

Indications for ureteroscopy include evaluation of filling defects within the upper urinary tract and after positive results on cytologic study or after noting unilateral gross hematuria in the absence of a filling defect. Ureteroscopy is also performed as a surveillance procedure in patients who have undergone conservative surgery for removal of a ureteral or renal pelvic tumor [18]. However, ureteroscopy is not necessary in all cases of suspected upper tract tumors. Ureteroscopy should probably be reserved for situations in which the diagnosis remains in question after conventional radiographic studies and for those patients in whom the treatment plan may be modified on the basis of the ureteroscopic findings, for example, endoscopic resection [18].

Flexible ureteroscopy is particularly useful in diagnostic uncertainty, if kidney-sparing treatment is considered, or in patients with a solitary kidney [1]. Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualization and diagnosis of flat lesions. Narrow-band imaging is a promising technique, but results are preliminary [1]. Table 14.1 shows summary of optimal imaging technique in UTUC.

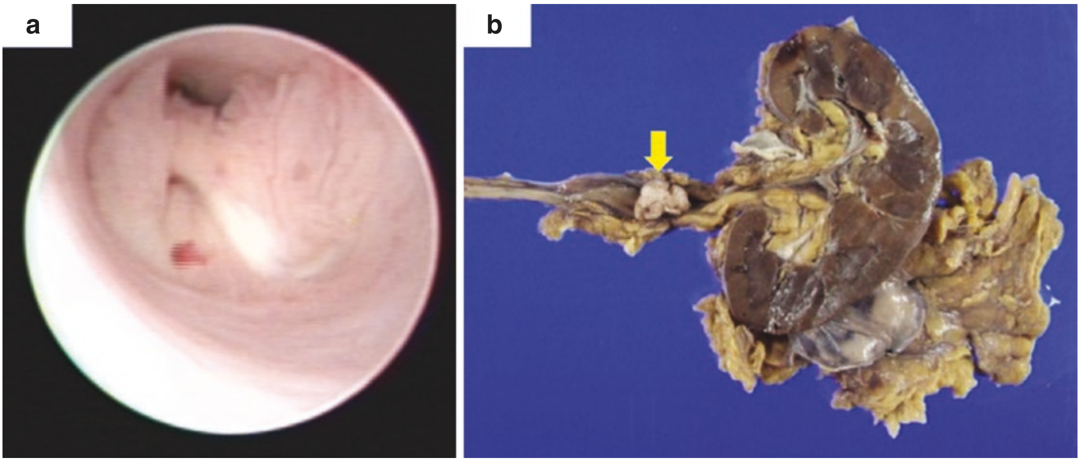

**Fig. 14.7** (**a**) Papillary mass in ureteroscopy. (**b**) Intact nephroureterectomy specimen with upper ureter tumor in the same patient. The patient showed low-grade urothelial cell carcinoma without invasion to muscularis

**Table 14.1** Summary of optical imaging techniques in the diagnosis of UTUC

| Technique | Principle | Purpose |
|---|---|---|
| Narrow-band imaging | Absorption | Better visualization |
| Storz professional image enhancement system | Absorption | Better visualization |
| Photodynamic diagnosis | Fluorescence | Better visualization |
| Optical coherence tomography | Scattering | Real-time information on tumor stage and grade |
| Confocal laser endomicroscopy | Absorption and reflection | Real-time information on tumor grade |
| Endoluminal ultrasonography | Absorption and reflection | Real-time information on tumor grade |

#### 14.4.2.1 Intravesical Recurrence and Diagnostic Ureteroscopy

Some researchers demonstrated that there might be a potential risk of tumor seeding caused by URS [26, 27]. Various hypotheses have been suggested to explain the intravesical recurrence (IVR) following the RNU, including intraluminal tumor seeding, intraepithelial cancer migration, and urinary tract cancerization [28, 29]. Recently, Lee et al. suggested that delayed nephroureterectomy after diagnostic ureteroscopy should be avoided to prevent intravesical recurrence [30]. However, the effects of preoperative diagnostic URS on the IVR following the RNU in patients with UTUC remained controversy. Moreover, there was general consensus among the study that treatment of UTUC should not be delayed.

### 14.4.3 Antegrade Endoscopy (Percutaneous Approach)

In some cases of upper tract tumors, percutaneous access to the renal pelvis may be required for diagnosis or treatment [1]. In such cases, antegrade urography and uroscopy may be useful for tumor resection, biopsy, or simple visualization. Indeed, EAU guideline recommended that percutaneous management can be considered for low-risk UTUC in the renal pelvis [1]. However, risk of tumor cell implantation in the retroperitoneum and along the nephrostomy tube tract must be considered before planning current procedure [18, 31]. This method is described in the endoscopic management of the nephron-sparing treatment part later.

## 14.5 Prognostic Factor of Recurrence and Progression

Generally, UTUC has poor prognosis and is often advanced when diagnosed. The low prevalence rate compared with UBC and poor overall survival make it difficult to establish a model to predict the prognosis of the patient. Most prognostic studies of UTUC are limited to retrospective studies, which also have a small sample size. Nonetheless, various studies have published results of prognostic factors which predict prognosis before or after surgery.

### 14.5.1 Preoperative Factor

#### 14.5.1.1 Age, Ethnicity, and Gender

Recently, gender is no longer considered an independent prognostic factor influencing UTUC mortality [1, 32]. However, older age at the time of radical nephroureterectomy (RNU) is independently associated with decreased cancer-specific survival (CSS) [1]. However, age alone is an inadequate indicator of UTUC prognosis. Population-based studies have indicated that African-American patients have worse outcomes than other ethnicities. However, there was controversy among the findings [1].

#### 14.5.1.2 Smoking

As like UBC, history of smoking is known that has correlation with poor prognosis of UTUC. Recent meta-analysis presented that smoking was correlated with intravesical recurrence [32]. In addition, smoking is significantly associated with advanced disease stages, disease recurrence, and cancer-specific mortality in patients treated with RNU for UTUC [33]. Current smokers and those with a heavy and long-term smoking exposure have the highest risk for poor oncologic outcomes. There is a correlation between tobacco consumption and prognosis; smoking cessation improves cancer control [1].

#### 14.5.1.3 Tumor Location

There remains disagreement as to whether the location of an upper tract tumor affects prognosis. However, initial location of the UTUC is a prognostic factor in some studies. After adjustment for the effect of tumor stage, patients with ureteral and/or multifocal tumor seem to have a worse prognosis than renal pelvic tumor [34–37]. Park et al. presented in their study which evaluates about the prognostic relevance of the ureteral location of the tumor only in patients with pT3 disease that renal parenchyma may have a protective role in patients with a pT3 tumor of the renal pelvis [38]. These findings were confirmed by a recent multi-institutional study, which presented that location of tumor in the ureter independently correlated with worse survival outcomes.

However, recent large multi-institutional studies did not confirm the independent prognostic impact of tumor location on survival, showing the same RFS and CSS estimates for renal pelvis and ureteral tumors after adjustment for several clinicopathologic factors [34]. So there is still need for a multicenter prospective study evaluating the differences in survival between patients with renal pelvis tumors and ureteral tumors.

#### 14.5.1.4 Surgical Delay

Surgical delay between diagnosis of tumor and its removal may increase the risk of disease progression [1]. In previous study, surgical delays are not associated with poor prognosis. However, excluding neoadjuvant chemotherapy and endoscopic management of UTUC, Lee et al. presented that surgical wait time longer than 1 month correlated with cancer-specific survival (HR 6.261, $p = 0.003$) [39].

#### 14.5.1.5 Clinical Staging

Unlike bladder cancer, the clinical staging of UTUC is notoriously difficult because biopsies that include underlying muscle are generally not possible because the ureter has thin muscle layer and it is a difficult delicate biopsy with relative small instrument used in ureteroscopy. Guarnizo et al. presented that UTUC has risk of 45% rate of upstaging with attempted clinical staging alone [40]. Imaging has risk of under-staging (16.2%) or did not detect (24.3%) and poor predictive value except in the assessment of significant locoregional extension or the presence of metastasis [34]. In conclusion, clinical tumor staging is generally unreliable except in advanced disease; however, biopsy tumor grading provides important variable that guides clinical management and predicts prognosis [34].

#### 14.5.1.6 Previous or Synchronous Bladder Cancer

UTUC can be considered as part of a panurothelial disease that can occur in multifocal tumors and transcend from the lower to the upper collecting system [34]. Mullerad et al. demonstrated in their multivariate analysis that a history of UBC had correlation with lower RFS and CSS of patients with UTUC [41]. In addition, Novara et al. presented in their large multicenter study that prior UBC history and the presence of muscle-invasive UBC at RNU were independent predictors of worse CSS [42].

#### 14.5.1.7 Chronic Kidney Disease

Chronic kidney disease (CKD) is known as independent prognostic factor of cardiovascular mortality, all-cause mortality, and non-cardiovascular mortality. CKD patients with UTUC are at risk at doubling of the serum creatinine levels and/or the occurrence of end-stage renal disease necessitating dialysis following unilateral RNU, and these circumstances would lead to deferred administration of adjuvant chemotherapy [43]. Recently, in large case series of study, CKD is associated with recurrence-free survival, cancer-specific survival, and overall survival [44]. Therefore, clinicians should keep in mind that preoperative renal status has implications in counseling for postoperative renal function and planning of chemotherapy in patients with UTUC.

#### 14.5.1.8 Other Preoperative Factors

Some study obesity and higher body mass index (BMI) is correlated with cancer-specific outcomes in UTUC [45]. Ehdaie et al. in their retrospective study that includes 520 patients treated with RNU for UTUC presented that higher body mass index (30 kg/$m^2$ or greater) is associated with worse recurrence-free (HR 3.52, $p < 0.001$), cancer-specific (HR 4.13, $p < 0.001$), and overall survivals (HR 2.33, $p < 0.001$) in patients treated with RNU for UTUC.

Neutrophil-to-lymphocyte ratio (NLR)-based markers are emerging as prognostic factor of UTUC. The pretreatment-derived NLR is correlated with higher cancer-specific mortality (HR 1.16, $p = 0.045$) in UTUC [46]. Otherwise, in posttreatment setting, Kang et al. demonstrated in their meta-analysis that a higher post-adjuvant chemotherapy NLR was independently predictive of poor CSS and OS in patients with advanced UTUC receiving systemic adjuvant chemotherapy after RNU [47].

### 14.5.2 Postoperative Factor

#### 14.5.2.1 Stage

Stage is currently the most important predictor of survival in patients with upper tract urothelial tumors. UTUCs that invade the muscle wall usually have a poor prognosis. Because of anatomical difference from the bladder, UTUC can spread easily by direct invasion, mucosal seeding, and hematologic and lymphatic routes. Prognosis decreases as stage increases, and the most significant decrease-free survival is observed in T3 tumors that have penetrated into the perirenal or periureteral fat [18]. EAU guideline presented that the 5-year-specific survival is <50% for pT2/pT3 and <10% for pT4 [1].

#### 14.5.2.2 Grade

Until 2004, the 1973 World Health Organization (WHO) classification which distinguished among three grades was a commonly used classification for urothelial cell carcinoma [48]. However, as mentioned above, the 2004 WHO classification considers histological data to distinguish between noninvasive tumors papillary urothelial neoplasia of low malignant potential and low- and high-grade carcinomas (low grade versus high grade) [49]. Several researchers validated the prognostic value of this newer classification and concluded that tumor grade represents a powerful predictor of cancer-specific outcomes in patients with UTUC [50–52]. High-grade tumor has more potent invasion into the underlying connective tissue, muscle, and surrounding tissues. In addition, high grade are also more likely to be associated with concomitant carcinoma in situ [18].

#### 14.5.2.3 Concomitant CIS

As in bladder cancer, it is known that CIS of the upper tract is associated with a poor prognosis and has potential future development of invasive urothelial cancers [18]. Some researchers demonstrated the concomitant CIS is correlated with RFS and CSS in patients with organ-confined UTUC [53, 54]. In addition, Otto et al. presented that concomitant CIS was associated with more advanced tumor stage and grade [54]. Therefore, the presence of a concomitant CIS should always be concerned in UTUC, because they may require more aggressive surveillance regimens and strategies treatment.

#### 14.5.2.4 Lymph Node Involvement

EAU guideline indicated that lymph node metastases and extra-nodal extension are powerful prognosis factor of survival outcomes in UTUC [1]. Depending on the primary tumor stage, 20–40% of patients show lymph node metastasis [55, 56]. Several studies presented an important detrimental effect of lymph node involvement on CSS, with a 5-year survival rate of approximately 30% in patients with lymph node metastases [34]. Specifically, patients with a lymph node density over 30% were at higher risk of disease recurrence and mortality. Therefore, lymph node dissection (LND) should be performed at the time of RNU allowing for optimal tumor staging; however its curative role remains controversial [1, 55].

#### 14.5.2.5 Lymphovascular Invasion

Lymphatic vessels contribute as the primary pathway for metastatic tumor cell spread in many types of cancer. Therefore, the presence of LVI in primary tumor may help identify patients without lymph node involvement who are at increased risk of cancer recurrence and mortality despite radical surgery [34]. Lymphovascular invasion (LVI) has been suggested to be an independent prognostic factor for disease-specific survival in UTUC. EAU guideline presented that LVI is present in approximately 20% of UTUCs and is an independent predictor of survival [1]. In addition, LVI correlated with tumor grade stage, lymph node status, and tumor necrosis [18]. Ku et al. demonstrated in their meta-analysis that LVI is correlated with disease-free survival (pooled HR, 1.91; 95% confidence interval [CI], 1.40–2.41), cancer-specific survival (CSS) (pooled HR, 1.72; 95% CI, 1.28–2.71), and overall survival (pooled HR, 4.05; 95% CI, −0.44 to 8.53). Therefore, EAU recommended that LVI status should be specifically reported in the pathological reports of all UTUC specimens.

#### 14.5.2.6 Surgical Margin

The presence of positive surgical margins (PSM) is reported in ≤8.5% of RNU cases and strictly depends on the management of the bladder cuff [34]. PSM after radical surgery or segmentectomy is reported as a significant factor for developing disease recurrence. Especially, PSM after RNU is an important prognostic factor for developing UTUC metastases [57]. EAU guideline recommended that pathologists should look for and report positive margins at the level of ureteral transection, bladder cuff, and around the tumor if over T2 stage [1]. However, correlation with PSM with CSS remains controversial.

#### 14.5.2.7 Tumor Multifocality

Tumor multifocality is reported that can be seen in >30% of UTUC cases [58]. Several investigators suggested in their retrospective case series that tumor multifocality is associated with poor prognosis in UTUC patients [42, 58, 59]. Especially, patients with a multifocal UTUC showed a threefold higher risk of cancer-specific mortality relative to patients without tumor multifocality.

### 14.5.3 Molecular Markers

The molecular biology and genetic basis of UTUC seem to be similar to that of TCCs of the bladder. Several studies evaluated the prognostic role of various tissue-based markers that are related to cellular processes such as cell adhesion, angiogenesis, cell proliferation, and apoptosis. However, because of the low prevalence of UTUC, these studies are limited to small size sample studies or retrospective studies. Furthermore, the fact that the markers for the expression of several markers have not yet been established is also a limiting factor. Multi-institutional efforts are still needed to determine the usefulness of molecular markers in the clinical decision-making process.

#### 14.5.3.1 p53

Since the first report of the possibility of a prognostic role by Rey et al., many investigators have reported that p53 is associated with the aggressive type of UTUC [60]. More recently in Japanese single-center study ($n$ = 66) and a European single-center study ($n$ = 53), while p53 was a predictor of survival in univariable analyses, it was not revealed as an independent prognostic factor after adjustment for other clinical and pathologic characteristics [61, 62].

#### 14.5.3.2 Ki-67

Ki-67 is a protein involved in cell proliferation. Some retrospective studies presented that overexpression of Ki-67 is associated with advanced tumor stage and higher grade and is an independent predictor of survival in patients with UTUC [63, 64]. In a recent meta-analysis, overexpression of Ki-67 was significantly associated with worse DFS (HR, 2.74; 95% CI, 1.58–4.74), CSS (HR, 2.26; 95% CI, 1.70–3.01), and OS (HR, 3.71; 95% CI, 1.78–7.75), but not intravesical recurrence-free survival (HR, 0.77; 95% CI, 0.10–5.82) [65]. However, there were still needed large, well-designed, prospective studies to establish the prognostic value of Ki-67 in UTUC.

#### 14.5.3.3 Epidermal Growth Factor Receptor

Epidermal growth factor receptor (EGFR) is strictly related to cell growth, proliferation, and differentiation. Leibl et al. demonstrated in their retrospective study (268 patients) that overexpression of EGFR is correlated with advanced clinicopathologic finding and metaplastic differentiation but not with CSS in multivariable analysis [66]. Recently, Long et al. also suggested in their immunohistochemistry analysis that negative EGFR is revealed as protective factor for preventing intravesical recurrence after intravesical treatment [67]. Moreover, the multivariate analysis revealed that EGFR positivity was an independent risk factor for recurrence after intravesical chemotherapy.

#### 14.5.3.4 E-cadherin

Decreased expression of E-cadherin has been reported as a feature of epithelial-mesenchymal transition (EMT) in epithelial malignancies [68]. Some reports presented that reduced E-cadherin expression is an independent predictor of prognosis in their multivariate analysis [69–71]. However, because of the rarity of UTUC, the main limitations of the above studies are their retrospective design and small sample size. Moreover, since the E-cadherin expression standards are different for each study, the results are contradictory for each study.

#### 14.5.3.5 Overexpression of Hypoxia-Inducible Factor-1α

HIF-1α is a transcription factor that plays an important role in cellular hypoxia adaptation. In a retrospective study of patients with UTUC, positive expression of HIF-1α was found in two thirds of cases. HIF-1α was significantly associated with advanced stage, lymph node invasion, tumor grade, and cancer-specific survival in multivariate analysis [72].

#### 14.5.3.6 Other Markers

Although there are still controversies between studies, many researchers are studying the prognostic value of various markers. Table 14.2 summarizes the prognostic value of various markers.

**Table 14.2** Summary of the result of studies about prognostic value molecular marker in UTUC patients

| Marker | Base | Detection | Function | Expression | Prognosis | Level of evidence |
|---|---|---|---|---|---|---|
| β-catenin [73] | Tissue | Immunohistochemistry | Cell adhesion | Loss | PFS, CSS | 3 |
| Parvin-β [74] | Tissue | Immunohistochemistry | Cell adhesion | Decreased | CSS | 3 |
| CD24 [75] | Tissue | Immunohistochemistry | Cell adhesion | Expression | Advanced stage, high grade | 3 |
| Uroplakin III [76] | Tissue | Immunohistochemistry | Cell differentiation | Loss | Advanced stage, CSS | 3 |
| Snail [77] | Tissue | Immunohistochemistry | Cell differentiation | Overexpression | Advanced stage, high grade, RFS, CSS | 3 |
| Bcl-2 [78] | Tissue | Immunohistochemistry | Apoptosis | Overexpression | Advanced stage, high grade | 3 |
| Survivin [78, 79] | Tissue | Immunohistochemistry | Apoptosis | Overexpression | Advanced stage, high grade, CSS | 3 |
| Telomerase mRNA [80] | Tissue | In situ hybridization | Maintaining DNA integrity | Overexpression | OS, RFS | 3 |
| Metalloproteinases [81, 82] | Tissue | Immunohistochemistry | Angiogenesis | Overexpression | Advanced stage, CSS | 3 |
| C-reactive protein [83, 84] | Blood | ELISA | Inflammatory response | Elevation | RFS, CSS | 3 |
| Leukocytes [85] | Blood | Cytometry | Inflammatory response | Elevation | RFS, CSS | 3 |
| Alkaline phosphatase [85] | Blood | Spectrophotometry | Hydrolase enzyme | Elevation | RFS, CSS | 3 |
| CYFRA 21-1 [86] | Blood | ELISA | Cell structural integrity | Elevation | OS | 3 |
| Microsatellite instability [87] | Genetic | PCR | Defect in DNA repair process | Microsatellite instability | CSS | 3 |
| Promoter hypermethylation [88] | Genetic | PCR | Repression of gene transcription | Promoter hypermethylation | Advanced stage | 3 |
| FGFR-3 [89] | Genetic | PCR | Cell proliferation and differentiation | Gene mutation | Better prognosis | 3 |

*CSS* cancer-specific survival, *RFS* recurrence-free survival, *OS* overall survival, *ELISA* enzyme-linked immunosorbent assay, *PCR* polymerase chain reaction, *FGFR-3* fibroblast growth factor receptor 3, *UTUC* upper tract urothelial carcinoma

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# 15

# Treatment of Upper Urothelial Cell Carcinoma

Bum Sik Tae and Chang Wook Jeong

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## 15.1 Neoadjuvant Treatment

Although the standard treatment for UTUC is RNU, evidence has steadily been growing regarding both neoadjuvant and adjuvant chemotherapy to have a role in treatment [1]. Matin et al. described that a significant reduction was seen in pathologic classification for patients who received neoadjuvant chemotherapy, including a 25.4% reduction in the incidence of pT2 or higher disease and a 41.5% reduction in the incidence of pT3 or higher disease [2]. In the subsequent studies, neoadjuvant chemotherapy was associated with a 14% complete remission rate and a significant rate of downstaging [3]. EAU guideline recommends that in perioperative chemotherapy for UTUC, there appears to be an overall and disease-free survival benefits for cisplatin-based chemotherapy (LE: 3) [1]. NCCN guideline also recommends that neoadjuvant chemotherapy should be considered in selected patients including condition with retroperitoneal lymphadenopathy, bulky (>3Cm) high-grade tumor, sessile histology, or suspected parenchymal invasion.

### 15.1.1 Indication

Indication for neoadjuvant chemotherapy for UTUC has not yet been established. Porten et al. began uniformly offering neoadjuvant chemotherapy to patients with UTUC who presented with high-risk features (such as patients who had overt evidence of clinical T4 disease or grossly involved lymph nodes) in their study [3]. Recently, Hosogoe et al. presented in their multinational study that neoadjuvant chemotherapy was safe and potentially improves oncological outcomes in locally advanced UTUC, including clinical T3–4 disease or local lymph node involvement (high-risk patients) [4]. However, major limitations of the neoadjuvant treatment include the probability that some patients may not tolerate both chemotherapy and surgery. Another obvious limitation of the neoadjuvant approach is the limited means of preoperative risk stratification and the possibility of overtreatment in some patients [2].

### 15.1.2 Protocol of Neoadjuvant Chemotherapy

Protocol for neoadjuvant chemotherapy for UTUC also has not yet been established. The first study presented by Igawa et al. included 15 patients who were treated either with MVAC (methotrexate, vinblastine, adriamycin, and cisplatin; $n = 5$), MEC (methotrexate, etoposide, and cisplatin; $n = 4$), or MVEC (methotrexate, vinblastine, epirubicin, and cisplatin; $n = 6$) before radical surgery [5]. Thereafter, several regimens with or without cisplatin were published. Recently, in prospective matched cohort study, patients received either gemcitabine 800 mg/m$^2$ on days 1, 8, and 15 plus cisplatin 70 mg/m$^2$ on day 2 every 3 weeks, or gemcitabine 800 mg/m$^2$ on days 1, 8, and 15 plus carboplatin at an area under the curve of 4 according to the Calvert formula on day 2 every 3 weeks, for 2–4 cycles [4]. There were no adverse effects of neoadjuvant chemotherapy for UTUC, although survival data need to mature and longer follow-up is awaited [1]. Two courses of neoadjuvant chemotherapy and surgery within 90 days in accordance with the recommendations for muscle invasive bladder cancer were effective in survival.

## 15.2 Radical Nephroureterectomy

RNU with excision of a bladder cuff is recommended for large, high-grade, invasive tumors of the renal pelvis and proximal ureter. Open RNU with bladder cuff excision is the standard for high-risk UTUC, regardless of tumor location [1]. RNU must comply with oncological principles, that is, preventing tumor seeding by avoidance of entry into the urinary tract during resection.

### 15.2.1 Open Approach

The choice of incision is mainly a matter of one of the surgeon's preference, surgeon's experience, the patient's body habitus and medical comorbidities, and the size of the kidney or tumor [6]. The operation can be performed through two incisions: one transverse upper abdominal and one lower abdominal (Gibson) incision. Alternatively, in non-obese patients, a single midline or paramedian abdominal incision may be used.

An extrapleural, extraperitoneal, thoracoabdominal incision is begun over the 11th or 12th rib or off the tip of the 12th rib. Torque flank position for RNU through a single thoracoabdominal incision may be applied. The shoulder girdle is rotated into a full-flank position. The pelvic girdle is rolled back nearly to a supine position. All potential pressure points are carefully padded. Adequate exposure to the kidney is the primary concern and the lower ureter and the bladder must also be exposed for nephroureterectomy. The RNU can be performed through an upper anterior subcostal incision and a lower quadrant Gibson incision. In addition, a lower midline incision can be substituted for bladder cuffing [6].

The nephrectomy portion of this operation is similar to the one described for radical nephrectomy with the exception that the ureter is not transected. The ureter should be dissected as low as possible. The authors prefer to leave the kidney and the ureter in situ to be removed as one anatomical piece to facilitate mapping of the specimen by the pathologist [7].

### 15.2.2 Laparoscopic Approach

Laparoscopic RNU is safe in experienced hands when adhering to strict oncological principles [1]. There is a tendency toward equivalent oncological outcomes after laparoscopic or open RNU [1, 8, 9]. However, there is concern about retroperitoneal metastatic dissemination and metastasis along the trocar pathway following manipulation of large tumors in a pneumoperitoneal environment [1]. Therefore, EAU guideline recommends several precautions to lower the risk of tumor spillage (Table 15.1).

#### 15.2.2.1 Trans-Peritoneal Technique

The patient is placed in modified flank position with the ipsilateral hip and shoulder rotated approximately 15–20°. The abdomen is insufflated, and three or four trocars are placed (Fig. 15.1). After insufflation, four or five trocars are placed for laparoscopic instrument. The primary 10/12-mm trocar is inserted at the lateral border of the rectus at the level of the umbilicus. For a right-sided nephrectomy, three

**Table 15.1** Several precautions for preventing tumor spillage

| |
|---|
| 1. Avoid entering or exposing the urinary tract |
| 2. Avoid direct contact between instruments and the tumor |
| 3. Laparoscopic RNU must take place in a closed system |
| 4. Avoid morcellation of the specimen and use an endo-bag for tumor extraction |
| 5. The kidney and ureter must be removed en bloc with the bladder cuff |
| 6. Invasive or large (T3/T4 and/or N+/M+) tumors are contraindications for laparoscopic RNU until proved otherwise |

*RNU* radical nephroureterectomy

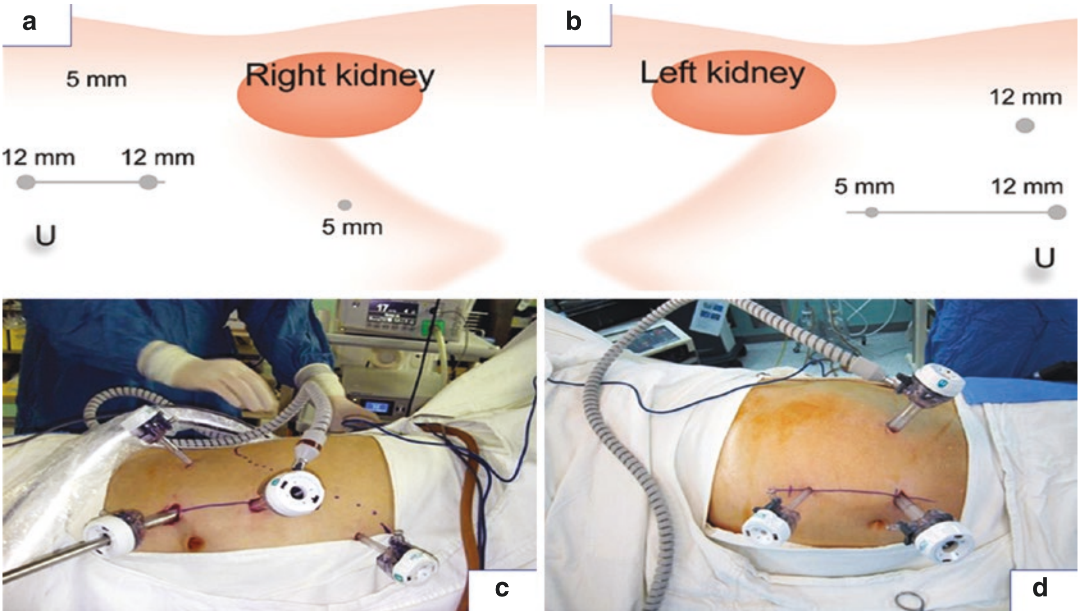

**Fig. 15.1** Port placement of laparoscopic radical nephroureterectomy. (**a**) Port placement of right side. 12 mm camera port placed in umbilicus level at rectus margin. Additional 5 mm port (optional) was placed near the xyphoid process. (**b**) Port placement of left side. (**c**) The patient is positioned on the table in a modified lateral decubitus position with the ipsilateral flank rotated up 15° for right-side nephroureterectomy. (**d**) Patient positioning and port placement for left-side nephroureterectomy

secondary trocars are placed: a 10/12-mm port for the laparoscopic approach 2–3 fingerbreadths below the costal margin at the lateral border of the rectus, a 5-mm port 2–3 fingerbreadths lateral to the rectus muscle at the costal margin, and a 5-mm port for lateral retraction of the kidney at the anterior axillary line. For a left-sided nephrectomy, a 5-mm port is placed at the lateral border of the rectus near the costal margin. In a right-sided nephrectomy, a 5-mm port is inserted near the xyphoid or posterior axillary line for retraction of the liver (Fig. 15.2). If a hand-assisted laparoscopic approach is chosen, the hand port site should be placed at Gibson incision location so that it can be used for the dissection of the distal ureter and open bladder cuff as indicated [6].

To reflect colon medially, dissect posterior peritoneum with energy device or electronic surgical scissor along white line of Toldt. Dissection includes hepatic flexure in right nephrectomy or splenic flexure in left nephrectomy. After colon medialization, anterior Gerota's fascia over the kidney is exposed. After identifying gonadal vessel, follow the gonadal vessel (with minimal ureter touch) and carefully dissect enough hilar fat to expose the renal artery and vein outside from the renal hilum. Make a window in the connective tissues around the renal vessels. Clip artery with two or three 10 mm clips proximally and one or two clips distally and divide renal artery. After dividing the renal artery, the renal vein is controlled with an Endo-GIA stapler (US Surgical, Norwalk, CT) or weck clips. After hilar control (before renal vein ligation or after renal vein ligation), find the ureter and clip it distally from suspicious tumor location to avoid tumor spillage or intravesical recurrence. After nephrectomy, the ureter should be dissected as low as possible avoiding direct manipulation of ureter and tumor. In this step, clinicians should keep in mind that the blood supply of ureter is generally anteromedially located in the proximal third, medially located in the middle third, and laterally located in the distal third [6].

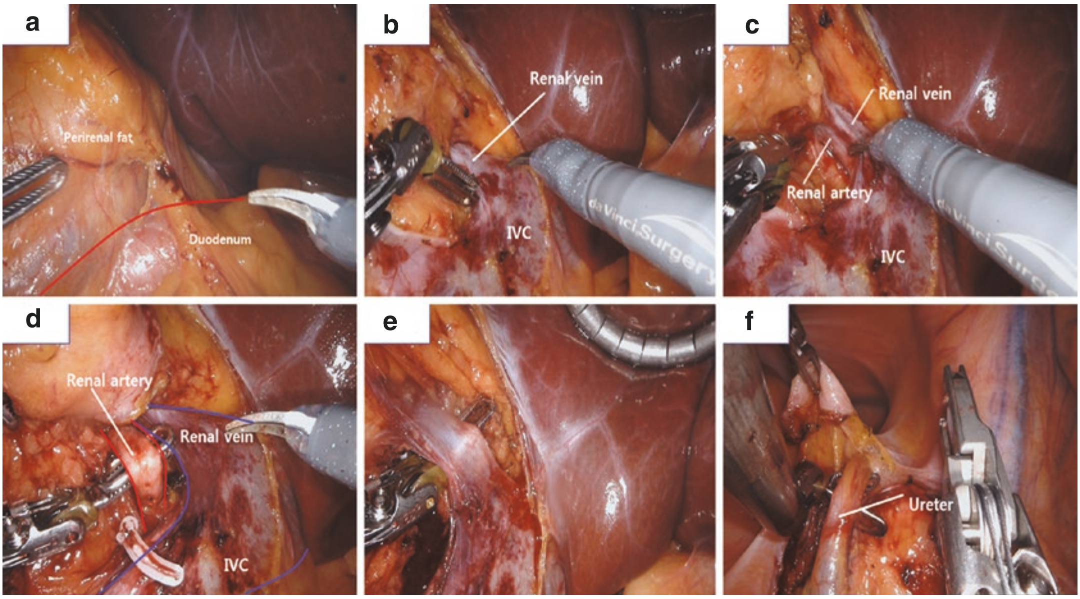

**Fig. 15.2** Step for right-side laparoscopic radical nephroureterectomy. (**a**) Take down large bowel and duodenum. (**b**) Find the right renal vein from IVC. (**c**) Perform skeletalization of renal artery. (**d**) Perform ligation and transection of renal artery. (**e**) Perform ligation and transection of renal vein. (**f**) Find the ureter and clip without transection. Early clipping of ureter prevents ureter seeding to the bladder

### 15.2.2.2 Retroperitoneal Technique

The patient's positioning is similar to the transperitoneal laparoscopic approach or full flank position. To secure working space, a commercially available trocar-mounted preperitoneal distention balloon (PDB) (Covidien Ltd., Mansfield, MA) is commonly used and the balloon has a maximum capacity of 800 mm. If there is no equipment, balloon dilator can be made with a surgeon's glove mounted on a No. 8 red rubber catheter. To place the balloon dilator, open (Hasson) technique is the most commonly employed because it affords the greatest precision during the development of the retroperitoneal space [6]. Initial access is obtained through a 1.5–2.0-cm transverse incision in the midaxillary line, just below the tip of the 12th rib. Under direct vision, the posterior layer of the lumbodorsal fascia is incised and muscle fibers are split or divided. The retroperitoneal space is entered, under direct vision, by making a small incision in the anterior thoracolumbar fascia with an electrocautery blade or, less commonly, by bluntly piercing the fascia digitally or with a hemostat [6]. Finger dissection is performed anterior to the psoas muscle and fascia to create a space for insertion of the balloon dilator. Confirmation that the finger dissection is indeed being performed in the proper plane is obtained by palpating the psoas and erector spinae muscles between the retroperitoneally located index finger and the fingertips of the opposite hand positioned on the patient's back [6]. And balloon dilator was placed in the retroperitoneal space via finger guide. Thus, balloon dilation is performed anterior to the psoas muscle and fascia and outside and posterior to the Gerota's fascia (Fig. 15.3).

Port placement can be performed by either three-port approach or four-port approach. The primary 12-mm port (camera port) is placed inferior to the tip of the 12th rib. An anterior 12-mm port is placed near the anterior axillary line 3 cm cephalad to the iliac crest. A posterior 5-mm port is placed at the junction of the lateral border of the paraspinal muscles and the 12th rib.

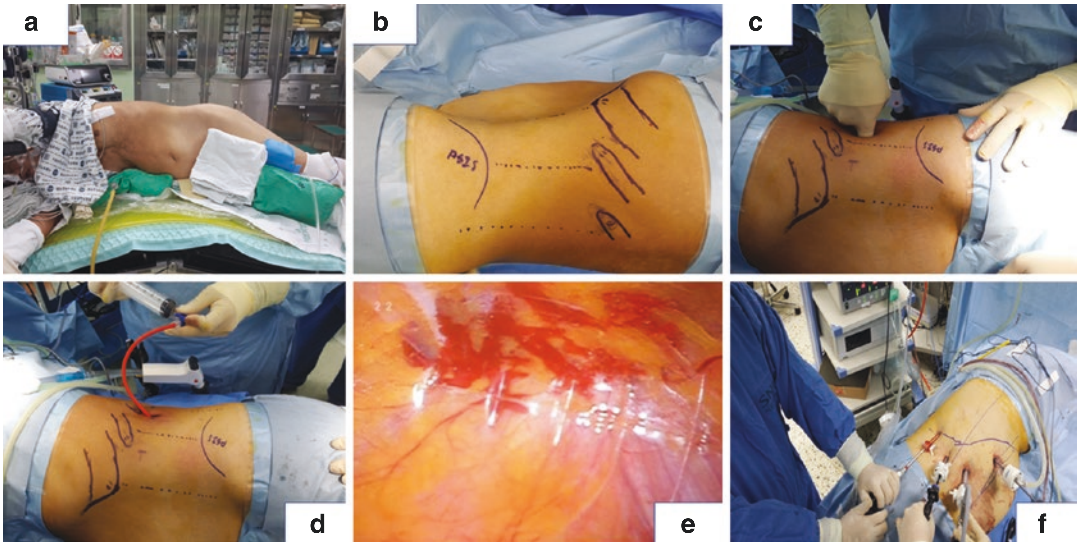

**Fig. 15.3** Patient's positioning and port placement of retroperitoneal approach. (**a**) The patient is positioned in the standard full-flank position. (**b**) Find the lateral border of the paraspinal muscles along the inferior border of the lowermost (12th) rib. (**c**) Finger dissection is performed to secure retroperitoneal space. (**d**) Self-made balloon dilator is a size seven surgeon's glove mounted on a No. 8 red rubber catheter. The external end of the catheter was connected to a sphygmomanometer bulb insufflator, and the balloon was insufflated to 110 mmHg. (**e**) A commercially available trocar-mounted preperitoneal distention balloon (PDB) (Covidien Ltd., Mansfield, MA) is used. Camera can actually be inserted into the shaft of the balloon dilator during the inflation process which provides the capability for endoscopic confirmation of the proper positioning of the transparent balloon and of the adequacy of the controlled radial dilation of the extraperitoneal area. (**f**) Port placement of retroperitoneal laparoscopic surgery

### 15.2.3 Oncological Outcomes: Open Versus Laparoscopic Approach

Recently, laparoscopic RNU has emerged as a minimally invasive alternative to open RNU, with advantages in terms of lower blood loss, shorter length of hospital stay, and shorter convalescence. Several investigators suggested in their retrospective studies that there was no significant difference in oncological outcomes between laparoscopic RNU and open RNU in well-selected patients [10, 11]. In addition, recent single-institutional randomized study confirmed these findings, showing no differences in progression-free survival and CSS between the open and laparoscopic approach in patients with organ-confined UTUC [12]. However, open approach is more beneficial than laparoscopic approach in patients with locally advanced UTUC (≤T3) or high-grade tumors. In addition, open approach may be considered in patients with locoregional disease at preoperative clinical staging or by surgeons without adequate laparoscopic experience.

### 15.2.4 Robot-Assisted Approach

Robotic-assisted laparoscopic nephroureterectomy (RALNU) is an extension of the pure laparoscopic technique taking advantage of the features of the robotic platform over those of standard laparoscopy. These enhancements include additional degrees of freedom with wristed instruments, motion scaling, and 3-dimensional visualization. These features make isolation of the distal ureter and bladder closure more feasible with the robotic surgical platform compared to pure laparoscopic surgery. Several techniques have been described for robotic radical nephroureterectomy using the da Vinci Si system including repositioning of the robot and/or patient or without patient repositioning or robot redocking [13]. The introduction of the most recent da Vinci Xi robotic system comes with an ability to alter orientation without changing ports and positioning. Therefore, this chapter describes our experience and technique of RALNU using the da Vinci Xi system [14]. The procedure is described in the enclosed video file (https://www.youtube.com/watch?v=-Bi6Cqxv31g&feature=youtu.be).

#### 15.2.4.1 Positioning and Port Placement

The patient is in a modified flank position with the diseased side up and then flexed using the table break at the level of anterior superior iliac crest. Upper arm is tucked to the patient's side. To avoid neuropraxia, pad is placed at all pressure points. Argun et al. described their port placement as follows [14]. After establishment of pneumoperitoneum, initial 8-mm port is placed 3 cm lateral to the umbilicus. The second 8-mm port is placed lateral to the rectus sheath and 8 cm cranial to the camera port. The third 8-mm port is placed caudal to the camera port on the same line and the fourth 8-mm port is placed approximately 15 cm lateral to the camera port and 2 cm caudal to the lower pole of the kidney. A 12-mm assistant port is placed on the midline, 5 cm cranial to the umbilicus. For tumors on the right side, an additional 5-mm port needs to be placed close to the xiphoid or lateral border of midaxillary line for liver retraction. Robot system is docked perpendicular to the bed over the backside of the patient. Instruments utilized for procedure are: monopolar curved scissors (right hand), fenestrated bipolar (left hand), and ProGrasp forceps. Suturing is performed with two large needle drivers. However, we used both redocking technique with Si system and single docking technique with Xi system. Our port placement of robotic nephroureterectomy (Seoul National University Hospital Technique) is described in Fig. 15.4.

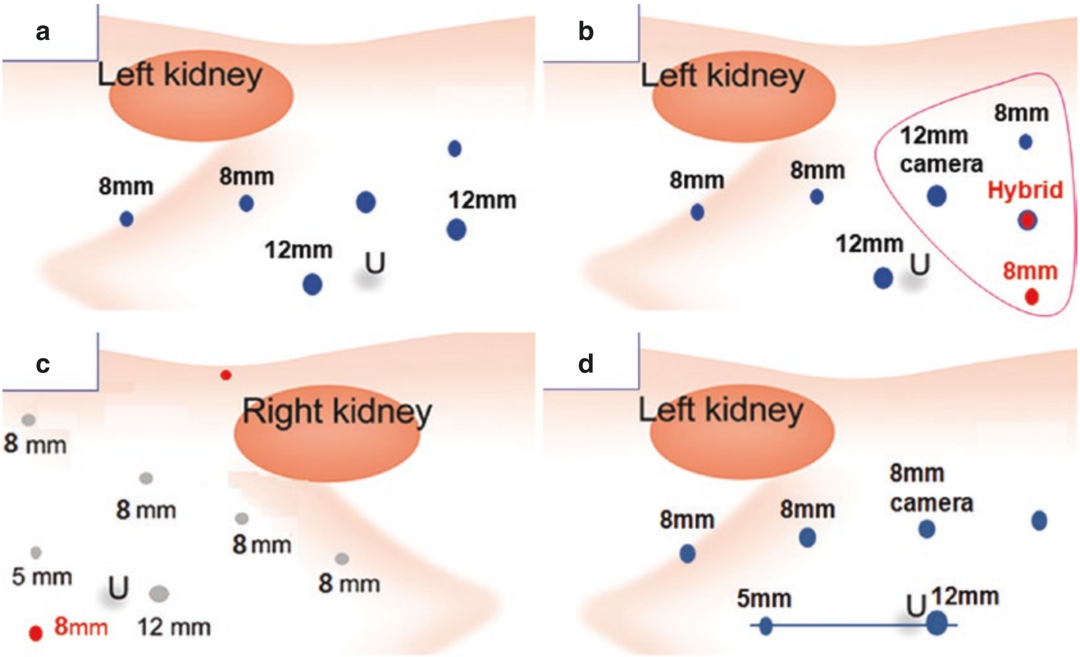

**Fig. 15.4** Port placement of robotic radical nephroureterectomy (RNU). (**a**) Port placement of RNU for left kidney. (**b**) Port placement of RNU for left distal ureterectomy and bladder cuffing. Hybrid port is one of the techniques that 12-mm port to be intubated with an 8-mm robotic port. (**c**) Port placement of single docking technique with Xi system in right RNU. (**d**) Port placement of single docking technique with Xi system in left RNU

#### 15.2.4.2 Surgical Procedure

Like laparoscopic RNU, dissection is started by incising the white line of Toldt lateral to the colon and mobilizing the colon medially. After complete mobilization of the colon, the lower pole of the kidney is identified. Following up along with gonadal vessel makes identification of renal vein and artery easy. The renal artery and vein are identified and divided using a vascular stapling device or clip. Upward traction on Gerota's fascia and the lower pole tissues will allow identification of the gonadal vein, ureter, and psoas muscle. The ureter is dissected from surrounding structures, and a clip is placed on the ureter below the level of the tumor (Fig. 15.5).

Upon completion of nephrectomy and lymphadenectomy, attention is then directed to the distal ureterectomy portion of the procedure. Not like laparoscopic RNU, we intracorporeally perform distal ureterectomy and bladder cuffing using robot, we usually do not completely mobilize the kidney at this point for better traction. All robotic arms are released and reconfigured for the distal ureteral dissection. The robotic crane is positioned to the lower pelvis. The third and second robotic arms are switched between the camera port and the fourth port. The second port continues to hold the fenestrated bipolar forceps, whereas Prograsp forceps is moved to the first port, and hot scissors to the third port. This reconfiguration of instruments facilitates the management of both the distal ureter excision and the bladder cuff reconstruction. During bladder cuff suturing, a large needle driver is placed into the right hand (Port #4). A 30-degree lens is used during the entire case. The specimen may be extracted by making a midline, Pfannenstiel or Gibson incision incorporating the most caudal port (Fig. 15.6).

## 15.3 Management of Distal Ureter and Bladder Cuff

Successful distal ureterectomy with a bladder cuffing is necessary for nephroureterectomy. General principles of bladder cuffing include intact complete ureteral excision with controlled occlusion of the ureteral orifice. The entire distal ureter, including the intramural portion and the ureteral orifice, must be removed [6]. If the entire distal ureter and ureteral orifice is not removed, it is associated with a high rate of tumor recurrence [1]. We should keep in mind that TCC is a tumor that has the potential to seed peritoneum or other space and that maintenance of a "closed system" is important, especially with high-grade tumors [6].

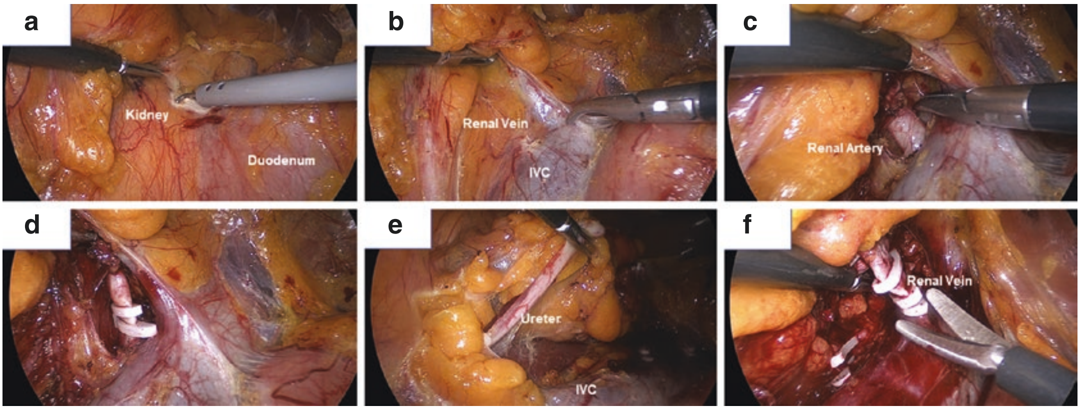

**Fig. 15.5** Surgical step for right side laparoscopic radical nephroureterectomy (part 1. Nephrectomy). (**a**) Take down large bowel and duodenum (**b**) Find the renal hilum (**c**) Find the renal artery behind the renal vein (**d**) Perform skeletalization of renal artery and transection (**e**) Find the ureter and clipping without transection. Early clipping of ureter prevents ureter seeding to the bladder (**f**) Perform skeletalization of renal vein and transection

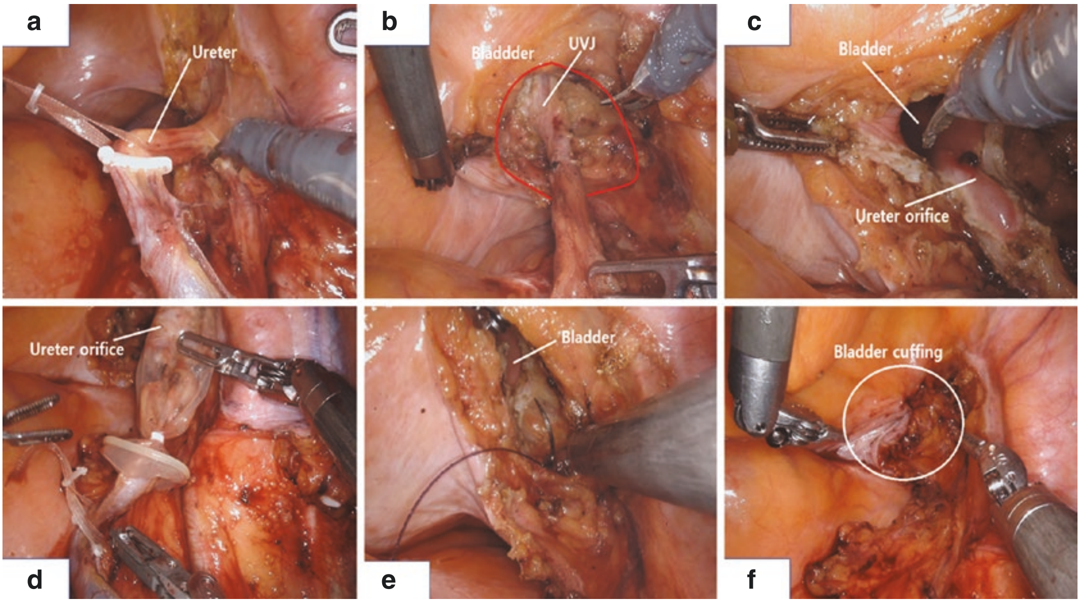

**Fig. 15.6** Surgical step for robotic RNU (part 2. distal ureterectomy with bladder cuffing). (**a**) Dissection along the ureter (**b**) Exposure of ureteral vesical junction (UVJ) (**c**) Bladder opening and dissection of UVJ and ureteral opening (**d**) Entrapment of the distal ureter and UVJ with entrapment lap sac (**e**) Suturing with absorbable suture (**f**) Bladder filling test

### 15.3.1 Open Technique

Open distal ureterectomy with bladder cuffing is the gold standard of management in NUx. This operation can be done through Gibson, Pfannenstiel, or low midline incisions, depending on the tumor location and the extent of proximal ureteral dissection required. It can also be divided into transvesical methods, extravesical methods, or combined methods, depending on whether the bladder is open or not. Among them, transvesical method is the most reliable approach for ensuring complete ureteral excision. An anterior cystotomy may be made and intravesical and extravesical dissection is performed as for ureteral neocystostomy, 1 cm of bladder mucosa is included circumferentially around the ureteral orifice. The defect in the bladder wall at the ureteral orifice is closed in two layers from within the bladder with interrupted 2-0 or 3-0 absorbable suture on the muscle and with or without 4-0 suture on the mucosa. Bladder opening site is closed in two or three layers with running 3-0 absorbable suture (Fig. 15.7). However, extravesical method does not require cystotomy. The ureter is tented up, and the bladder mucosa is divided between clamps. The defect in the bladder wall is closed in layers, as described previously. Care must be taken to ensure a complete dissection of the intramural portion of the ureter and to avoid contralateral injury from excessive traction.

### 15.3.2 Laparoscopic Extravesical Technique

This method can be considered in laparoscopic radical nephroureterectomy. Flexible cystoscopy is performed before the laparoscopic portion of

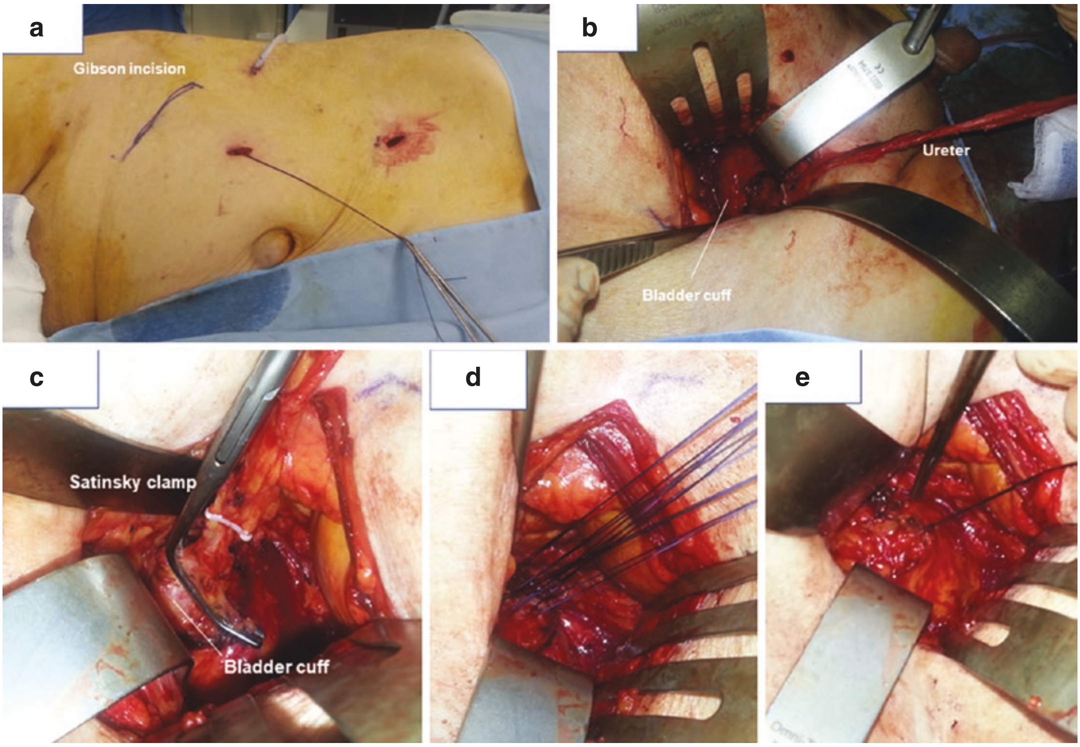

**Fig. 15.7** Open technique of distal ureterectomy with bladder cuffing. (**a**) Patient's positioning and Gibson incision was made (**b**) Exposure of bladder cuff and distal ureter (**c**) Satinsky clamp method. This method has the advantage of avoiding bladder opening. However, there is a potential disadvantage that it could not identify ureteral orifice (**d**) Bladder opening and stay suture technique. This method is able to identify ureteral orifice. However, there has a potential disadvantage that it could not maintain closed system (**e**) Bladder filling test after bladder repair

the surgery. And Bugbee electrode is used to cauterize the orifice and intramural ureter completely. Cauterization of the intramural portion of the ureter helps identify the distal end of the dissection during the laparoscopic portion of the surgery. After nephrectomy and ureter dissection down to the detrusor muscle, antegrade traction is placed on the ureter, everting the orifice out of the bladder, and an endovascular stapling device (EndoGIA, AutoSuture, Norwalk, CT) or Ligasure Atlas device (Valleylab, Tyco Healthcare UK, Gosport, UK) is placed as distally as possible. Flexible cystoscope can be placed to ensure that the entire ureter is removed.

This method has the advantage that it does not require additional incision for bladder cuff. However, a retrospective study reported that the laparoscopic stapling technique is associated with greater positive margin and local recurrence rates than the open or transvesical approaches [15]. In addition, there is a theoretical risk of stone encrustation along the staple line, as well as a risk of compromising the contralateral hemitrigone with stapler placement.

### 15.3.3 Endoscopic Resection

#### 15.3.3.1 Open Versus Endoscopic Techniques

About 50 years ago, ureteral intussusception and extraction by way of the urethra is an option for ureterectomy in radical nephroureterectomy. However, recurrences (intravesical recurrence 22.6%, locoregional recurrence 3.1%) were significantly greater in the ureteral intussusception group compared to open method. In addition, successful ureteral intussusception requires an immobilized lumbar ureter. Thus, the routine use of the ureteral stripping technique during LNU is not recommended [16]. Up to date, various endoscopic excision methods have been used to facilitate the dissection of the distal ureter.

Among the endoscopic approaches, the pluck technique had at least five reported cases of local recurrence or tumor seeding, and the stripping technique showed a higher rate of intravesical disease recurrence [17]. In addition, several retrospective studies showed that stapling of the bladder cuff was associated with a higher risk of positive margins and recurrence [9, 15]. However, some researchers suggested that other endoscopic techniques of bladder cuff showed similar cancer-control outcomes in comparison with a formal open technique. However, it is still controversial that current findings were mostly based on small retrospective studies. Finally, a bladder-cuff removal at RNU has to be considered the gold standard treatment for UTUC regardless of the tumor stage and location and open management of bladder cuff should be considered the gold standard technique [18].

#### 15.3.3.2 Transurethral Resection of Ureteral Orifice

This method has the advantage of its ability to avoid second incision in performing a nephroureterectomy. However, since this procedure should be done in the lithotomy position, most patients are placed in the lateral position, which means that they have to change their positioning. In addition, various concerns exist regarding the oncologic efficacy of this approach. First, the potential for incomplete resection of the intramural ureter exists; thus, current approach is not recommended in patients with distal ureteral tumors [19]. Second, because of the multifocality of TCC, there is the potential risk of extravesical seeding, even in the absence of known distal tumors.

First, patients are placed in the lithotomy position and undergo rigid cystoscopy with aggressive resection of the ureteral orifice and intramural ureter into the perivesical fat. After procedure, patients are then repositioned for radical nephronureterectomy. Once the proximal specimen is mobilized, the previous transurethral resection eases the subsequent bladder cuff excision.

As mentioned above, transurethral approach has the potential of tumor seeding. To decrease this risk, modified transurethral approach was suggested that performing transurethral resection at the conclusion of the procedure, in conjunction with hand-assisted laparoscopic nephroureterectomy (HALNU), might decrease the likelihood of tumor spillage and thereby result in more favorable long-term oncologic outcomes [20–22]. This technique involves early ligation of the proximal ureter before distal ureteral excision, further decreasing the potential for tumor spillage. To avoid repositioning issue, flexible cystoscope and Bugbee electrode during radical nephroureterectomy should be performed [22]. Current approach has the disadvantage of technical difficulty of endoscopic resection using a flexible cystoscope and Bugbee electrode. Although the hand port aids in the dissection, precise resection might be more difficult than in techniques involving rigid endoscopy. And current approach has no advantage over the pure laparoscopic approach.

Modified transurethral approaches are implemented in the following manner. A 1-cm bladder cuff around the ipsilateral ureteral orifice is excised using the cutting current of a 5F Bugbee electrode. Throughout this portion of the procedure, the surgeon's hand, by way of the hand port, can be used to stabilize the bladder and help in the resection. The cystostomy is typically not sutured closed, and a Foley catheter is placed in place for 5–7 days until cystography is performed to exclude a bladder leakage [16].

#### 15.3.3.3 Cystoscopic Detachment and Ligation

Gill et al. initially described transvesical detachment and ligation technique in 1999 [23]. The patient is placed in the dorsal lithotomy position and two 2-mm needlescopic ports are inserted into the bladder suprapubically using cystoscopic guidance. Next, a 2-mm (or 3 mm) Endoloop is placed through one of the ports such that the loop surrounds the ureteral orifice of interest. And guide wire and 6F ureteral catheter were then placed into the ureteral orifice up to the renal pelvis. The ureter is tented up, and a loop ligature is placed around the catheter and the orifice, creating a “closed” system. Bladder cuff excision was performed under 24F resectoscope with a Collins knife placed alongside the ureteral catheter. The bladder excision site is not closed, and a Foley catheter is placed for 2 weeks.

The current method has some potential advantages. First, it is most closely to the oncologic principles of open nephroureterectomy. Second, the ureteral catheter minimizes the risk of inadvertent entry into the intramural ureter and subsequent incomplete resection of the distal ureter. In addition, occlusion of the ureteral lumen using Endoloop and electrocautery helps to minimize the risk of tumor cell seeding to perivesical space. However, it can be technically difficult. And, patients with concomitant or recent bladder tumors were considered at high risk of tumor seeding with the transvesical needlescopic technique. Lastly, this technique should not be used in obese patients or those with a history of pelvic surgery or radiotherapy because of the risk of improper suprapubic port placement [23].

### 15.3.4 Pneumovesical Laparoscopic Approach

Pneumovesical laparoscopic method has been applied in various urology fields and has the advantage of excellent visibility, less morbidity, and improved cosmesis [24]. Recently, this approach has been applied to bladder cuffing procedure. Cheng et al. first described using a transvesical pneumovesical laparoscopic method for managing the distal ureter during laparoscopic radical nephroureterectomy (Fig. 15.8) [25]. First, the bladder is distended with saline under cystoscopy and the laparoscopic port is then inserted under a cystoscopy guide, and the bladder is inflated with $CO_2$ while draining the saline [24]. Additional two 5-mm trocars are inserted as working ports, and a 5-mm trocar for the midline camera port that houses a 0° 5-mm telescope [26]. As soon as the bladder cuff and intramural ureter are dissected, Endoloop knot is used to ligate the ureter to avoid tumor spillage and aid in the identification of the ureter during final laparoscopic extraction. The bladder defect site is closed in two layers with a 2-0 (or 1-0) absorbable polyglactin suture.

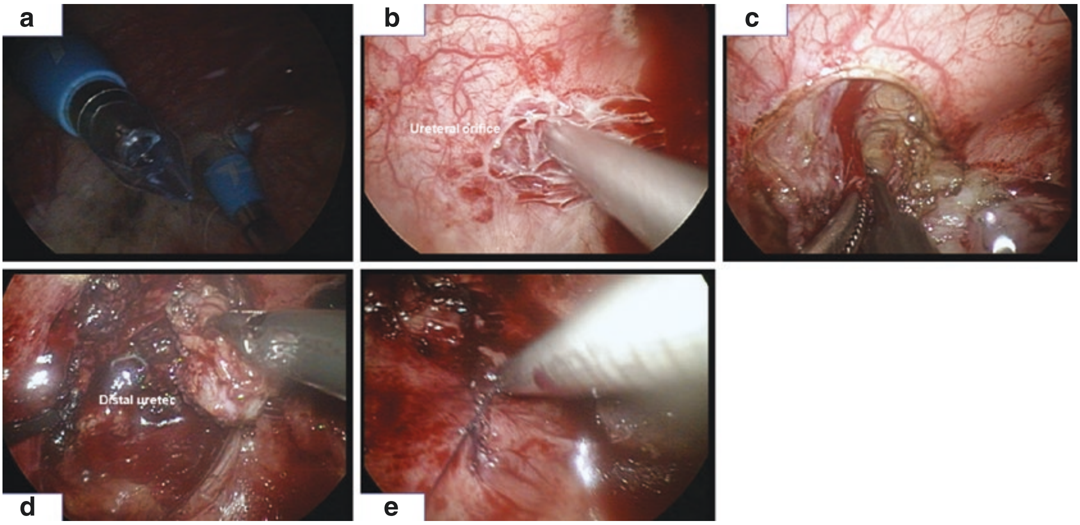

**Fig. 15.8** Pneumovesical laparoscopic approach of bladder cuffing. (**a**) Port insertion. The laparoscopic ports are inserted under a cystoscopy guide, and the bladder is inflated with $CO_2$. Two 3- or 5-mm trocars are used for the working ports, and a 5-mm trocar for the midline camera port that houses a 0° 5-mm telescope. (**b**) Identification of ureteral orifice and dissection along submucosal ureter (**c**) Dissection of submucosal ureter and muscle layer (**d**) Excision of bladder cuff (**e**) Bladder cuff is sutured using absorbed suture

The current method has several theoretical advantages, including en bloc removal of the entire specimen, excellent visualization of the bladder and minimization of the potential for tumor seeding with early closure of the distal ureteral orifice, and the use of $CO_2$ gas instead of fluid irrigation [24]. In addition, this method does not require additional incision for bladder cuffing, so it improves recovery time and minimizes bladder spasms and hematuria. However, there is no long-term follow-up study of oncologic outcome. In addition, the theoretical risk for tumor seeding during port insertion is also present [24]. Lastly, current approach should be avoided if patients showed urothelial cancer in the intramural ureter or have a history of overactive bladder or pelvic irradiation.

## 15.4 Lymphadenectomy

### 15.4.1 Regional Lymphadenectomy Templates for UTUC

To date, the role of regional lymphadenectomy for patients with UTUC remains incompletely defined, with inconsistent utilization of regional retroperitoneal lymph node dissection (LND) and no standardization of the approach [1]. The use of an LND template is likely to have a greater impact on patient survival than the number of removed lymph nodes.

Kondo et al. published an update of the data described above, and further highlighted the nodal sites where the incidence of metastasis was greater than 30%. So they proposed a template for complete regional LND for UTUC (Fig. 15.9) [27].

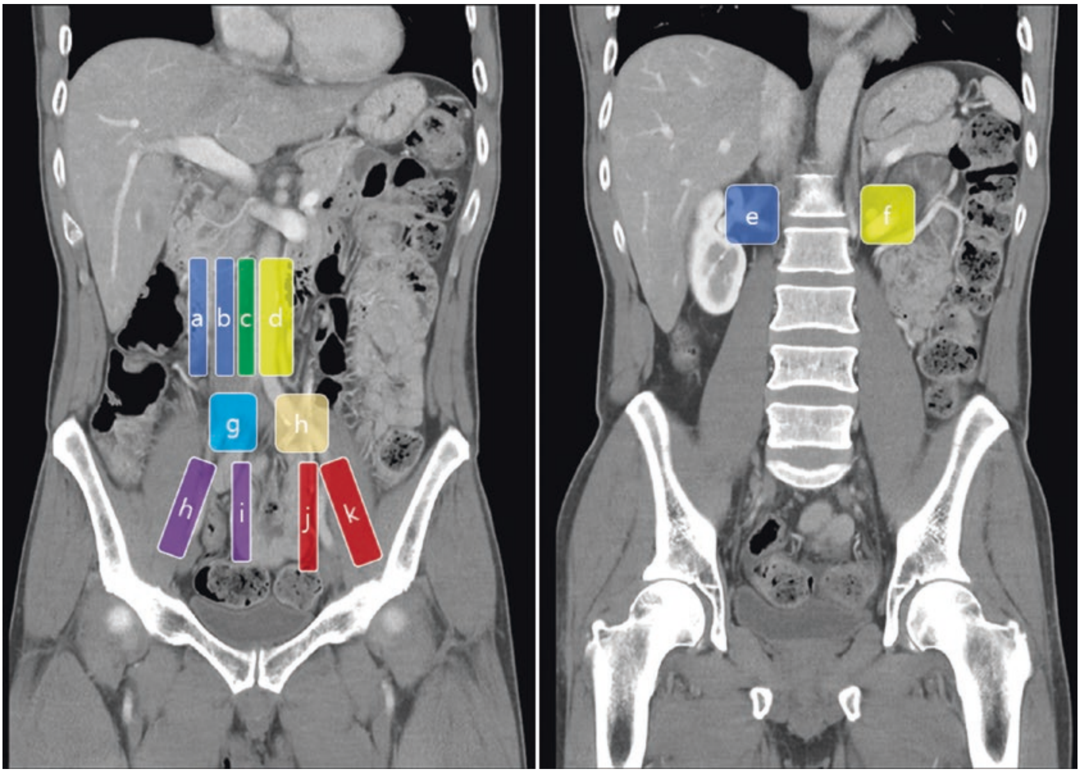

**Fig. 15.9** Image of the regional lymph nodes according to the location of the primary tumors. If tumor is located in the right renal pelvis, lymphadenectomy includes a, b and e; left renal pelvis includes d and f; right upper 2/3 ureter includes a, b, c and e; left upper 2/3 ureter d and f; left lower 1/3 ureter includes g, h and I; left lower 1/3 ureter includes h, j and k. (a) paracaval (b) retrocaval (c) inter-aortocaval (d) para-aortic (e) right renal hilar (f) left renal hilar (g) right common iliac (h) right external iliac (i) right internal iliac and obturator (j) left internal iliac and obturator (k) left external iliac lymph nodes

Above all, the extent of lymphadenectomy should be determined by the template, and not by the number of nodes removed.

Kondo et al. demonstrated that tumors of the right renal pelvis should have renal hilar, paracaval, and retrocaval lymph node packets removed. For UTUC of the upper two-thirds of the right ureter (above the level of the common iliac artery), the renal hilar, paracaval, retrocaval, and inter-aortocaval lymph node packets should be removed. Conversely, for left-sided tumors of the renal pelvis and upper two-thirds of the ureter, the renal hilar and para-aortic nodes should be removed. Finally, for tumors of the lower third of the ureter, the authors recommend removal of the ipsilateral common iliac, external iliac, internal iliac, and obturator lymph node packets. In addition, a template is based on the laterality and location of the primary tumor, and the template for tumors of the lower ureter is similar to that for the ipsilateral extended LND performed for bladder cancer [27].

### 15.4.2 Staging Role

LND appears to be unnecessary in cases of TaT1 UTUC because lymph node retrieval is reported in only 2.2% of T1 versus 16% of pT2–4 tumor [1, 28]. Therefore, an increase in the probability of lymph node positive disease is related to pT staging. However, it is likely that the true rate of node positive disease has been under-reported because these data are retrospective. If the value of regional lymphadenectomy lies in helping to appropriately select patients for adjuvant chemotherapy, then the benefit of such therapy in the setting of known lymph node positive disease must be considered [29]. However, there are no randomized trials that provide evidence to definitively support the value of adjuvant chemotherapy for lymph node positive UTUC [1].

The presence of nodal involvement represents a poor prognostic indicator, significantly affecting patient outcome [30]. LND allows adequate postoperative patient counseling and risk stratification, thereby identifying patients for a risk-adapted approach such as close follow-up or adjuvant chemotherapy. In a large multinational study, the 5-year cancer specific survival estimate was significantly lower in patients with lymph node positive compared with those with pNx disease, which in turn was lower than in patients with pN0 disease [31]. Especially in T2–T4, cancer specific survival was lowest in pN+ patients, intermediate in pNx, and highest in pN0. pN+ was an independent predictor of reduced cancer specific survival, and pNx was significantly associated with worse prognosis than pN0 in pT2–4 UTUC only. This study suggested that LND should always be performed in patients with muscle invasive or more advanced disease to better discriminate patients with a high risk of progression and death who might benefit from adjuvant systemic therapy [31].

As an extension of the bladder cancer literature, LN density is also noticed as a valuable prognostic tool for risk stratification of patients with nodal involvement in UTUC [32]. Bolenz et al. proposed that patients with a LN density over 30% were at a significantly greater risk of both recurrence and mortality than those with a LN density lesser than 30%. Because LN density is determined by the proportion of the number of positive LNs and the number of LNs removed and examined, such findings reinforce the hypothesis of the usefulness of LND for both staging and potential therapeutic purposes.

### 15.4.3 Therapeutic Role

Many authors presented that prognostic advantage for patients undergoing LND who had no evidence of lympho-vascular invasion [33, 34]. Nonetheless, because this parameter is not known until the definitive pathology, these findings are not helpful to indicate LND during surgery. In a retrospective study, actuarial 5-year DFSs were 64% and 37% in patients with muscle invasive UTUC who underwent LND or did not, respectively [35]. An accurate LND could remove some nodal micro-metastasis not identified on routine pathologic examination, thus improving locoregional control and cancer specific survival. Radical surgery and LND might be curative in a subpopulation with limited nodal disease, as described in bladder cancer. LND may reduce the residual tumor burden in patients who are candidates for adjuvant chemotherapy [36]. Some authors demonstrated that a number of LNs were emerged as an independent predictor of both disease free survival and cancer specific survival. But an established number of LNs removed is not enough to optimize survival, as demonstrated by Koppie et al. for bladder cancer [37].

## 15.5 Nephron-Sparing Surgery

### 15.5.1 Open Segmental Ureterectomy

#### 15.5.1.1 Ureteroureterostomy

In low-grade tumors of proximal ureter or mid-ureter that are too large for complete endoscopic ablation, segmental ureterectomy with uretero-ureterostomy can be considered. However, even if high-grade or invasive tumors, when nephron-sparing for preservation of renal function is a goal, segmental ureterectomy and ureteroureterostomy can also be indicated. When tumor locates in the proximal ureter, modified flank position can be applied for procedure. However, if the tumor is in the mid-ureter, supine position with a roll under the ipsilateral lumbar space is suitable. To provide good exposure to the mid-ureter, angular extraperitoneal incision from the tip of the 12th rib toward the pelvis should be made. The ureter is identified, mobilized, and secured with vessel loops proximally and distally. The tumor is palpated, and the ureter is ligated 1–2 cm proximal and distal to the tumor. The most important thing is avoiding tumor violation or tumor spillage. And the involved ureteral segment is excised and sent for frozen-section analysis to confirm the diagnosis, grade, and stage and to verify that both resection margins are tumor free. If possible, a regional lymphadenectomy is performed. The ureter is repaired by mobilizing both ends to allow a tension-free anastomosis. Ureteroureterostomy is possible if there is a defect of up to 4 cm in length, but if there are more defects, other procedures should be considered. With maintaining periureteral blood supply, the ureteral ends are spatulated and anastomosed with interrupted absorbable 4-0 (or 5-0) sutures. A ureteral stent is placed as the anastomosis is in progress, and a closed-suction drain is placed in the retroperitoneal space near but not touching the repair.

#### 15.5.1.2 Distal Ureterectomy and Direct Neocystostomy or Ureteroneocystostomy with a Bladder Psoas Muscle Hitch or a Boari Flap

If the tumor locates in the distal ureter which cannot be removed completely by endoscopic procedure, distal ureterectomy with neocystostomy can be considered [6]. The indication of the current method is larger, high-grade, organ-confined or suspicious invasive tumor.

In the supine position, Gibson, Pfannenstiel, or lower midline incision can be applied to expose the distal ureter and bladder for the ureteral excision and the repair [6]. First, the distal ureterectomy is performed as mentioned above. There should be concern about spillage of known tumor in the distal ureteral segment. However, there was no consensus about standard technique of ureteroneocystostomy. The anti-refluxing anastomosis technique may prevent infections as well as seeding of the upper tract with tumors from the bladder. However, refluxing anastomosis may be more beneficial when considering follow-up procedures such as imaging studies or ureteroscopy.

If only short distal ureter segmentectomy is performed, direct ureteroneocystostomy can be applied. However, additional techniques are required when the entire distal ureter is sacrificed [6]. Bladder psoas muscle hitch technique is the first treatment of choice in this case. To release the tension of anastomosis site, superior vesical attachments on the opposite side of the bladder are taken down. Then, the bladder is mobilized upward over the iliac vessels to the psoas muscle at the level of the iliac crest. Note the damage of the genitofemoral nerve, bladder is secured to the psoas muscle and tendon with a row of interrupted 2-0 absorbable sutures.

And then, anterior cystotomy is made for ureteroneocystostomy. The ureteral end is spatulated and brought through an opening in the cystostomy portion of the bladder. The anti-refluxing anastomosis is completed with interrupted 4-0 absorbable sutures. In addition, the anterior cystotomy site is closed in two layers with 3-0 absorbable suture.

If a greater gap which is not sufficient in psoas hitch technique must be bridged, Boari flap technique combined with a psoas muscle hitch can help reach the proximal ureter. Boari flap is another method of bridging a longer gap of up to 10 cm (12–15 cm). After detachment of contralateral bladder pedicle, the flap continues obliquely across the anterior bladder wall, with the base of the flap being at least 4 cm in width and the tip of the flap being at least 3 cm in width [6]. The flap length should equal the estimated ureteral defect plus an addition of 3–4 cm if an anti-refluxing anastomosis is planned. After bladder flap creation, the distal end of the flap is secured to the psoas minor tendon or psoas major muscle with 2-0 absorbable sutures. Distal end of ureter is passed through a small opening created in the posterior flap, and a tension-free mucosa to mucosa refluxing anastomosis is performed after spatulation of the distal ureteral end. If needed, anti-refluxing tunneled anastomosis can be applied. The bladder tube is folded and closed in two layers with running 3-0 absorbable suture.

## 15.5.2 Endoscopic Management

### 15.5.2.1 Ureteroscopic Management

In the past, endoscopic surgery for UTUC was recommended only for patients with imperative indications, such as renal insufficiency or a solitary functional kidney, bilateral disease, or a significant comorbidity that precluded radical surgery. Recently, EAU guideline recommends that endoscopic management can be considered in patients with clinically low-risk cancer. However, they recommend that endoscopic management should be considered only in the following situations [1]. First, laser generator and pliers are available for biopsies. Second, in case a flexible (rather than a rigid) ureteroscope is available. Third, the patient is informed of the need for early (second look), closer, more stringent, surveillance. Lastly, complete tumor resection or destruction can be achieved. Specially, Raman and Seisen et al. presented that the following features of low risk UTUC are potentially amenable to endoscopic ablation: (1) No active or prior bladder urothelial carcinoma, (2) No active occupational or lifestyle exposures, (3) Absence of hydronephrosis, (4) No sign of local invasion (5) Tumor size below 1 cm, (6) Single tumor, (7) Low-grade lesion on ureteroscopic biopsy, and (8) Negative urinary cytology [38, 39].

The most important step when considering conservative management of UTUC is accurate staging. Ureteroscopic biopsy provides the opportunity for adequate tissue sampling although the tools and yield are far more limited when compared to resection of bladder tumors. Indeed, while there is an 80–90% correlation between tumor grade on ureteroscopic biopsy and final surgical specimens at nephroureterectomy, the concordance with tumor staging is far less reliable [40, 41].

Tumors within the middle and distal ureter are generally accessible by semirigid ureteroscope while those in the proximal ureter, renal pelvis, or calyces necessitate flexible ureteroscopy. Ureteral access sheath can potentially decrease the intrapelvic pressure particularly during longer cases which may require continuous positive pressure irrigation [42, 43]. Biopsy instruments have improved over time with variants of cup biopsies and stone baskets able to procure often suitable for establishing a histologic diagnosis of UTUC albeit with limited capacity to assign stage [41, 44]. Recently, endoscopic ablation techniques generally describe an initial debulking with stone basket or cold cup followed by treatment with laser ablation (Holmium:YAG or Neodynium: YAG) or small electrocautery probes (2–3 Fr) [45–47]. Because the use of electrocautery has potential post procedure stricture and it typically requires use of a hypotonic irrigation solution which can have side effects if absorbed into the vascular system, laser ablation with Holmium:YAG laser has been emerging as ideal for laser ablation of UTUC tumors [38].

The upper tract recurrence in those treated with ureteroscopy ranged from 15 to 90%, while progression to radical surgery occurred in 3–33% [41]. The high recurrence rates emphasize the importance of adherence to a strict surveillance program. However, cancer specific survival remained high with 70–100%, while overall survival ranged from 35 to 100% depending on follow-up interval of this fairly comorbid patient population [38]. Finally, it does not appear that attempted ureteroscopic ablation for appropriate tumors necessarily impacts oncologic outcomes for those who progress to radical surgery.

#### 15.5.2.2 Percutaneous Endoscopic Management

The ureteroscopic retrograde approach has the benefit of conserving a closed urinary system. However, the percutaneous antegrade approach can also be considered for low-grade or noninvasive UTUC in the renal cavities [1]. Because of the use of the larger instrument, this method has the advantage of removing a slightly larger renal pelvis tumor. In addition, the percutaneous approach also allows better access to the lower caliceal system, which is inaccessible by flexible ureteroscopy.

After establishing percutaneous tract, the suspicious lesion is initially biopsied and subsequently debulked. Monopolar and bipolar electrocautery, rollerball electrodes, lasers, and electro vaporization instrument can be applied for tumor ablation. The base of the tumor lesion is separately resected and sent for staging. After procedure, hemostasis is achieved by laser ablation or electrocautery. If there is a need for repeated treatment or administration of topical adjuvant therapy, established nephrostomy tract can be maintained [41].

However, there is main concern about the potential of the increased morbidity compared with ureteroscopy and the potential for tumor seeding outside the urinary tract [6]. In addition, establishing nephrostomy procedure has also inherent risks which require additional admission. Thus, this approach has been used less due to the availability of improved endoscopic tools such as distal-tip deflection of recent ureteroscopy.

## 15.6 Adjuvant Treatment

Any nephron-sparing procedure has a higher local recurrence rate due to the established risk of ipsilateral recurrence. Several efforts have been made to minimize these risks and they were classified as basic categories: instillation of immunotherapeutic or chemotherapeutic agents and brachytherapy of the nephrostomy tract. However, after complete resection, the major concern about adjuvant treatment is to prolong OS and CSS.

### 15.6.1 Instillation Therapy

Instillation therapy can be performed in several ways. Accepted techniques include antegrade instillation through a nephrostomy tube and retrograde instillation directly into a ureteral catheter or by reflux in a patient with an indwelling ureteral stent or iatrogenically created vesicoureteral reflux [6]. Topical immunotherapy with Bacillus Calmette-Guerin (BCG) and chemotherapy with mitomycin C have been the mainstays of adjuvant topical therapy in urothelial cell carcinoma. Such topical agent has also been used after nephron-sparing management for UTUC to decrease recurrences [41]. Especially after endoscopic management in upper urinary tract, instillation can be performed through a percutaneous nephrostomy tube or via a retrograde ureteral catheter. The purpose of this therapy is continued exposure of the urothelium to the topical agent while maintaining a low pressure system that is free of infection.

#### 15.6.1.1 Anterograde Instillation

The most reliable access to the upper urinary tract remains via a nephrostomy tube large enough (e.g., 10 F) left in place after percutaneous endoscopic treatment, or placed under local anesthesia and in the prone position, under ultrasound guided. The agent is instilled by gravity and linked to a manometer to maintain intrarenal pressure below 25 cm $H_2O$ [48]. BCG therapy was the most common agent used, and Thalman et al. suggested a reproducible protocol [49]. A dose of 360 mg Immun BCG Pasteur® or 243 mg Immucyst® is dissolved in 150 mL 0.9% saline. And instillation agent is then placed 20 cm above the level of the kidney of the supine patient. A continuous flow of approximately 1 mL/min is maintained for 2 hours. After instillation, the nephrostomy is closed. Similar to the bladder cancer, BCG treatment is repeated on a weekly basis for 6 weeks. The major complication of instillation therapy is bacterial sepsis [6]. In addition, there is critical issue on significant breach of the integrity of the collecting system which can cause tumor recurrence through seeding of cancer cells [48].

#### 15.6.1.2 Retrograde Instillation

With the development of flexible digital ureteroscopes, combined with effective ablative laser technique, the retrograde approach has received considerable interest in recent years. If ureteral catheter was placed, topical agent can be delivered by retrograde reflux from the bladder with an indwelling double-J stent in Trendelenburg position [50]. Then, cystography is performed with the patient in the Trendelenburg position to confirm the volume necessary to cover the entire upper urinary tract system (range 80–250 mL, median 120 mL). Then the intravesical instillation of the agent is performed with the patient in the Trendelenburg position, held in position for 15–30 minutes and voided 30 minutes to 2 hours after instillation. The schedule for BCG includes a weekly instillation for 6 weeks.

The perfusion of BCG in the UUT by vesicoureteral reflux has the potential to cause an efficient immune reaction. The activation of an immune response is promoted by the attachment of the vaccine to the cancer cells or the urothelium and is rapidly developed by the stimulation of mononuclear cells [51]. Schneider et al. reported that the attachment of BCG to tumor cells and the stimulation of mononuclear cells could occur in a short time frame or even by mere contact [51].

### 15.6.2 Adjuvant or Immediate Intravesical Instillation After Radical Surgery

It is known that intravesical recurrence after radical surgery for UTUC is 22–47% [1]. Reduced intravesical recurrence correlates with the reduced risk of subsequent seeding into the contralateral ureter or reduced risk of renal failure from tumor or from damage to the contralateral ureteric orifice during bladder cancer surgery. One meta-analysis demonstrated that male gender, previous bladder cancer history, preoperative chronic renal disease, positive preoperative urinary cytology, tumor location, multifocality, invasive pT stage, necrosis, laparoscopic RNU, extravesical bladder cuff removal, and positive surgical margins correlate with intravesical recurrence [52]. To reduce intravesical recurrence, intravesical instillation has attracted attention. Recently, prospective randomized trials have demonstrated that a single postoperative dose of intravesical chemotherapy (mitomycin C, pirarubicin) soon after surgery reduces the risk of intravesical recurrence after radical surgery [53, 54]. Especially, early instillation within 24 hours after nephroureterectomy was associated with a significantly reduced rate of bladder recurrence [55]. In meta-analysis, the instillation agents including mitomycin C, hydroxycamptothecin, pirarubicin, and epirubicin seemed to be associated with similar treatment results. However, there is insufficient evidence to formally test whether any of the specific combinations of chemotherapy was more or less effective [56].

### 15.6.3 Adjuvant Chemotherapy

Like bladder cancer, UTUC seemed to be chemosensitive [6]. Extrapolating from the bladder cancer literature and small, single-center UTUC studies, platinum-based combination chemotherapy is expected to be efficacious in UTUC. However, the major limitation to long-term survival for patients with locally advanced upper tract tumors is distant relapse with metastatic disease [6]. Neoadjuvant and adjuvant systemic chemotherapy used for proven metastatic disease are reasonable. A recent study has assessed a clear survival benefit in patients who received adjuvant chemotherapy versus observation after RNU for pT3/T4 and/or lymph node positive UTUC [57]. However, there are currently insufficient data upon which to base recommendations [1].

In metastatic disease, the systemic chemotherapy regimens offered for treatment are the same as those used for transitional cell carcinoma of the bladder. There are several platinum-based regimens, but not all patients can receive adjuvant chemotherapy because of comorbidities and impaired renal function after radical surgery [1]. Chemotherapy-related toxicity, particularly nephrotoxicity due to platinum derivatives, may significantly reduce survival and quality of life in patients with postoperative renal dysfunction. Chemotherapy regimens are discussed in Chapter Treatment of Muscle Invasive Bladder Cancer (Section II. Muscle invasive and metastatic bladder cancer. Chap. 3 Treatment of Muscle Invasive Bladder Cancer). For additional improvements in treatment efficacy and safety, further experience with new chemotherapeutic regimens is needed.

### 15.6.4 Radiotherapy

The role of radiotherapy (RT) has not been clearly defined and studies have reported contradictory findings. Because of the rarity of UTUC, previous studies have been limited by the inclusion of a small number of patients in different disease stages and the use of old RT techniques, insufficient doses, and various surgical approaches. Some studies reported a low rate of local recurrence after adjuvant RT after surgical treatment, whereas others showed similar RFS between adjuvant-RT and surgery-alone groups, or even lower rates in the surgery-alone group [58–63]. Jwa et al. presented that 3-year actuarial RFS rates were 89% vs. 61% in the RT vs. non-RT groups, respectively [64]. In a largest retrospective study (252 patients), disease-specific and overall 5-year survival of UTUC treated with adjuvant RT was 41% and 28%, respectively, for patients with stage T3 disease. Actual 5-year disease-specific survival for stage T3 with or without adjuvant radiation therapy was 45% and 40%. Local relapse occurred in only 9% of the entire cohort and was seen only in patients with stage T3 and stage T4 disease. Therefore, EAU guidelines demonstrated that radiotherapy is no longer relevant, either alone or as an adjunct to chemotherapy [1].

## 15.7 Follow-up

### 15.7.1 Organ-Confined Disease

NCCN guidelines recommended that cystoscopy should be performed every 3 months for 1 year, then at increasing intervals. If endoscopic resection was performed, imaging of upper urinary tract collecting system or ureteroscopy at 3–12 months intervals with/without abdominal CT or MRI with or without contrast should be done.

Otherwise, EAU guidelines recommended that follow-up is more frequent and stricter in patients who have undergone kidney-sparing treatment compared to RNU (LE 3) [1]. Urine cytology and CT urography were performed at 3 and 6 months, and then annually. In addition, EAU guidelines recommended performing cystoscopy, ureteroscopy, and urine cytology at 3 and 6 months, and then every 6 months for 2 years, and then annually. Moreover, in cases of RNU, EAU guidelines recommended cystoscopy/urinary cytology at 3 months, and then annually (GR C). And CT urography is recommended every year.

### 15.7.2 Non-Organ-Confined Disease

NCCN guidelines suggested that adjuvant chemotherapy is considered in cases of non-organ-confined UTUC. In addition, cystoscopy is recommended every 3 months for 1 year, then at increasing intervals. However, if endoscopic management was performed, imaging of upper urinary tract collecting system or ureteroscopy at

3–12 months intervals with abdominal CT or MRI (with or without contrast) and chest imaging should be done. Moreover, EAU guidelines recommended that cystoscopy/urinary cytology should be performed at 3 months and then annually in invasive tumor. In addition, urography CT is recommended every 6 months for 2 years, and then annually.

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